(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number
WO 2004/083389 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number:
PCT/US2004/007626

(22) International Filing Date: 12 March 2004 (12.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/454,469	13 March 2003 (13.03.2003)	US
60/470,728	14 May 2003 (14.05.2003)	US
60/479,769	19 June 2003 (19.06.2003)	US
60/479,795	19 June 2003 (19.06.2003)	US

(71) Applicant *(for all designated States except US)*: **EXELIXIS INC.** [US/US]; 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FRANCIS-LANG, Helen** [GB/US]; 1782 Pacific Avenue, #2, San Francisco, CA 94109 (US). **WINTER, Christopher, G.** [US/US]; 641 Homer Avenue, Palo Alto, CA 94301 (US). **VENTURA, Richard, Benn, Abegania** [US/US]; 290 Bay Ridge Drive, Daly City, CA 94014 (US). **BJERKE, Lynn, Margaret** [US/US]; 728 Alabama Street, #201, San Francisco, CA 94110 (US). **ZHANG, HaiGuang** [US/US]; 4833 El Grande Place, El Sobrante, CA 94083 (US). **ADAMKEWICZ, Joanne, I.** [US/US]; 1249 Rhode Island Street, San Francisco, CA 94107 (US). **HAI, Bing** [CN/US]; 410 Promenade Lane, Redwood City, CA 94065 (US). **LICKTEIG, Kim** [US/US]; 1921 Grove Street, San Francisco, CA 94117 (US). **NICOLL, Monique** [US/US]; 224 Naomi Avenue, Pacifica, CA 94044 (US).

(74) Agents: **SHAYESTEH, Laleh** et al.; Exelixis, Inc., 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

(57) Abstract: Human MBCAT genes are identified as modulators of the beta-catenin pathway, and thus are therapeutic targets for disorders associated with defective beta-catenin function. Methods for identifying modulators of beta-catenin, comprising screening for agents that modulate the activity of MBCAT are provided.

WO 2004/083389 A2

MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional patent applications 60/454,469 filed 3/13/2003, 60/470,728 filed 5/14/2003, 60/479,795 filed 6/19/2003, and 60/479,769 filed 6/19/2003. The contents of the prior applications are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

The *Drosophila Melanogaster* Armadillo/beta-catenin protein is implicated in multiple cellular functions. The protein functions in cell signaling via the Wingless (Wg)/Wnt signaling pathway. It also functions as a cell adhesion protein at the cell membrane in a complex with E-cadherin and alpha-catenin (Cox et al. (1996) J. Cell Biol. 134: 133-148; Godt and Tepass (1998) Nature 395: 387-391; White et al. (1998) J Cell biol. 140:183-195). These two roles of beta -catenin can be separated from each other (Orsulic and Peifer (1996) J. Cell Biol. 134: 1283-1300; Sanson et al. (1996) Nature 383: 627-630).

In Wingless cell signaling, beta -catenin levels are tightly regulated by a complex containing APC, Axin, and GSK3 beta /SGG/ZW3 (Peifer et al. (1994) Development 120: 369-380).

The Wingless/ beta -catenin signaling pathway is frequently mutated in human cancers, particularly those of the colon. Mutations in the tumor suppressor gene APC, as well as point mutations in beta -catenin itself lead to the stabilization of the beta -catenin protein and inappropriate activation of this pathway.

The ability to manipulate the genomes of model organisms such as *Drosophila* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, Mechler BM et al., 1985 EMBO J 4:1551-1557; Gateff E. 1982 Adv. Cancer Res. 37: 33-

74; Watson KL., et al., 1994 J Cell Sci. 18: 19-33; Miklos GL, and Rubin GM. 1996 Cell 86:521-529; Wassarman DA, et al., 1995 Curr Opin Gen Dev 5: 44-50; and Booth DR. 1999 Cancer Metastasis Rev. 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the genetic entry point. When the genetic entry point is an ortholog of a human gene implicated in a disease pathway, such as beta-catenin, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in their entireties.

SUMMARY OF THE INVENTION

We have discovered genes that modify the beta-catenin pathway in *Drosophila*, and identified their human orthologs, hereinafter referred to as modifier of beta catenin (MBCAT). The invention provides methods for utilizing these beta-catenin modifier genes and polypeptides to identify MBCAT-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired beta-catenin function and/or MBCAT function. Preferred MBCAT-modulating agents specifically bind to MBCAT polypeptides and restore beta-catenin function. Other preferred MBCAT-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress MBCAT gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MBCAT modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MBCAT polypeptide or nucleic acid. In one embodiment, candidate MBCAT modulating agents are tested with an assay system comprising a MBCAT polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate beta-catenin modulating agents. The assay system may be cell-based or cell-free. MBCAT-modulating agents include MBCAT related proteins (e.g. dominant negative mutants, and

biotherapeutics); MBCAT -specific antibodies; MBCAT -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MBCAT or compete with MBCAT binding partner (e.g. by binding to an MBCAT binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate beta-catenin pathway modulating agents are further tested using a second assay system that detects changes in the beta-catenin pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the beta-catenin pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MBCAT function and/or the beta-catenin pathway in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MBCAT polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be administered to a mammalian animal predetermined to have a pathology associated with the beta-catenin pathway.

DETAILED DESCRIPTION OF THE INVENTION

In a screen to identify enhancers and suppressors of the Wg signaling pathway, we generated activated beta -catenin models in *Drosophila* based on human tumor data (Polakis (2000) Genes and Development 14: 1837-1851). We identified modifiers of the Wg pathway and identified their orthologs. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MBCAT genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective beta-catenin signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.

In vitro and in vivo methods of assessing MBCAT function are provided herein. Modulation of the MBCAT or their respective binding partners is useful for understanding the association of the beta-catenin pathway and its members in normal and disease

conditions and for developing diagnostics and therapeutic modalities for beta-catenin related pathologies. MBCAT-modulating agents that act by inhibiting or enhancing MBCAT expression, directly or indirectly, for example, by affecting an MBCAT function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MBCAT modulating agents are useful in diagnosis, therapy and pharmaceutical development.

Nucleic acids and polypeptides of the invention

Sequences related to MBCAT nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), shown in Table 1 and in the appended sequence listing.

The term "MBCAT polypeptide" refers to a full-length MBCAT protein or a functionally active fragment or derivative thereof. A "functionally active" MBCAT fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MBCAT protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MBCAT proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MBCAT polypeptide is a MBCAT derivative capable of rescuing defective endogenous MBCAT activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of an MBCAT, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MBCAT polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of an MBCAT. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MBCAT nucleic acid" refers to a DNA or RNA molecule that encodes a MBCAT polypeptide. Preferably, the MBCAT polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least

70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MBCAT. Methods of identifying orthlogs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD et al, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *Drosophila*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence

identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, Advances in Applied Mathematics 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, Genomics 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 Nucl. Acids Res. 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of an MBCAT. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing. Conditions routinely used are set out in readily available procedure texts (*e.g.*, Current Protocol in Molecular Biology, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, Molecular Cloning, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of an MBCAT under high stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is

0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 μg/ml herring sperm DNA; hybridization for 18-20 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 μg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 μg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 μg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

Isolation, Production, Expression, and Mis-expression of MBCAT Nucleic Acids and Polypeptides

MBCAT nucleic acids and polypeptides are useful for identifying and testing agents that modulate MBCAT function and for other applications related to the involvement of MBCAT in the beta-catenin pathway. MBCAT nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MBCAT protein for assays

used to assess MBCAT function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (e.g., Higgins SJ and Hames BD (eds.) Protein Expression: A Practical Approach, Oxford University Press Inc., New York 1999; Stanbury PF et al., Principles of Fermentation Technology, 2nd edition, Elsevier Science, New York, 1995; Doonan S (ed.) Protein Purification Protocols, Humana Press, New Jersey, 1996; Coligan JE et al, Current Protocols in Protein Science (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MBCAT is expressed in a cell line known to have defective beta-catenin function. The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding an MBCAT polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MBCAT gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MBCAT gene product, the expression vector can comprise a promoter operably linked to an MBCAT gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MBCAT gene product based on the physical or functional properties of the MBCAT protein in *in vitro* assay systems (*e.g.* immunoassays).

The MBCAT protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (i.e. it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein

synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

Once a recombinant cell that expresses the MBCAT gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MBCAT proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MBCAT or other genes associated with the beta-catenin pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

Genetically modified animals

Animal models that have been genetically modified to alter MBCAT expression may be used in *in vivo* assays to test for activity of a candidate beta-catenin modulating agent, or to further assess the role of MBCAT in a beta-catenin pathway process such as apoptosis or cell proliferation. Preferably, the altered MBCAT expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MBCAT expression. The genetically modified animal may additionally have altered beta-catenin expression (e.g. beta-catenin knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, i.e. mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (i.e., in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MBCAT gene that results in a decrease of MBCAT function, preferably such that MBCAT expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MBCAT gene is used to construct a homologous recombination vector suitable for altering an endogenous MBCAT gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989) 244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene,

may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH et al., (1994) Scan J Immunol 40:257-264; Declerck PJ et al., (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MBCAT gene, e.g., by introduction of additional copies of MBCAT, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MBCAT gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of Saccharomyces cerevisiae (O'Gorman et al. (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X et al (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the beta-catenin pathway, as animal models of disease and disorders implicating defective beta-catenin function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MBCAT function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MBCAT expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MBCAT function, animal models having defective beta-catenin function (and otherwise

normal MBCAT function), can be used in the methods of the present invention. For example, a beta-catenin knockout mouse can be used to assess, *in vivo*, the activity of a candidate beta-catenin modulating agent identified in one of the *in vitro* assays described below. Preferably, the candidate beta-catenin modulating agent when administered to a model system with cells defective in beta-catenin function, produces a detectable phenotypic change in the model system indicating that the beta-catenin function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

The invention provides methods to identify agents that interact with and/or modulate the function of MBCAT and/or the beta-catenin pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the beta-catenin pathway, as well as in further analysis of the MBCAT protein and its contribution to the beta-catenin pathway. Accordingly, the invention also provides methods for modulating the beta-catenin pathway comprising the step of specifically modulating MBCAT activity by administering a MBCAT-interacting or -modulating agent.

As used herein, an "MBCAT-modulating agent" is any agent that modulates MBCAT function, for example, an agent that interacts with MBCAT to inhibit or enhance MBCAT activity or otherwise affect normal MBCAT function. MBCAT function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MBCAT - modulating agent specifically modulates the function of the MBCAT. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MBCAT polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MBCAT. These phrases also encompass modulating agents that alter the interaction of the MBCAT with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MBCAT, or to a protein/binding partner complex, and altering MBCAT function). In a further preferred embodiment, the MBCAT- modulating agent is a modulator of the beta-catenin pathway (e.g. it restores and/or upregulates beta-catenin function) and thus is also a beta-catenin-modulating agent.

Preferred MBCAT-modulating agents include small molecule compounds; MBCAT-interacting proteins, including antibodies and other biotherapeutics; and nucleic

acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19th edition.

Small molecule modulators

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight up to 10,000, preferably up to 5,000, more preferably up to 1,000, and most preferably up to 500 daltons. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MBCAT protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products, particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MBCAT–modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below, can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the beta-catenin pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

Protein Modulators

Specific MBCAT-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the beta-catenin pathway and related disorders, as well as in validation assays for other MBCAT-modulating agents. In a preferred embodiment, MBCAT-interacting proteins affect normal MBCAT function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MBCAT-interacting proteins are useful in detecting and providing information about the function of MBCAT proteins, as is relevant to beta-catenin related disorders, such as cancer (e.g., for diagnostic means).

An MBCAT-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MBCAT, such as a member of the MBCAT pathway that modulates MBCAT expression, localization, and/or activity. MBCAT-modulators include dominant negative forms of MBCAT-interacting proteins and of MBCAT proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MBCAT-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3rd, Trends Genet (2000) 16:5-8).

An MBCAT-interacting protein may be an exogenous protein, such as an MBCAT-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MBCAT antibodies are further discussed below.

In preferred embodiments, an MBCAT-interacting protein specifically binds an MBCAT protein. In alternative preferred embodiments, an MBCAT-modulating agent binds an MBCAT substrate, binding partner, or cofactor.

Antibodies

In another embodiment, the protein modulator is an MBCAT specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be

used in screening assays to identify MBCAT modulators. The antibodies can also be used in dissecting the portions of the MBCAT pathway responsible for various cellular responses and in the general processing and maturation of the MBCAT.

Antibodies that specifically bind MBCAT polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MBCAT polypeptide, and more preferably, to human MBCAT. Antibodies may be polyclonal, monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab').sub.2 fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MBCAT which are particularly antigenic can be selected, for example, by routine screening of MBCAT polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Nati. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of an MBCAT. Monoclonal antibodies with affinities of 10^8 M^{-1} preferably 10^9 M^{-1} to 10^{10} M^{-1}, or stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MBCAT or substantially purified fragments thereof. If MBCAT fragments are used, they preferably comprise at least 10, and more preferably, at least 20 contiguous amino acids of an MBCAT protein. In a particular embodiment, MBCAT-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MBCAT-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MBCAT polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

Chimeric antibodies specific to MBCAT polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the

antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

MBCAT-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins

may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Specific biotherapeutics

In a preferred embodiment, an MBCAT-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MBCAT is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MBCAT, as described in the previous section, may be used as biotherapeutic agents.

When the MBCAT is a receptor, its ligand(s), antibodies to the ligand(s) or the MBCAT itself may be used as biotherapeutics to modulate the activity of MBCAT in the beta-catenin pathway.

Nucleic Acid Modulators

Other preferred MBCAT-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MBCAT activity. Preferred nucleic acid modulators interfere with the function of the MBCAT nucleic acid such as DNA replication, transcription, translocation of the MBCAT RNA to the site of protein translation, translation of protein from the MBCAT RNA, splicing of the MBCAT RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MBCAT RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MBCAT mRNA to bind to and prevent translation, preferably by binding to the 5′ untranslated region. MBCAT-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiamidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MBCAT nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known

in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al., Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MBCAT-specific nucleic acid modulator is used in an assay to further elucidate the role of the MBCAT in the beta-catenin pathway, and/or its relationship to other members of the pathway. In another aspect of the invention, an MBCAT-specific antisense oligomer is used as a therapeutic agent for treatment of beta-catenin-related disease states.

Assay Systems

The invention provides assay systems and screening methods for identifying specific modulators of MBCAT activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MBCAT nucleic acid or protein. In general, secondary assays further assess the activity of a MBCAT modulating agent identified by a primary assay and may confirm that the modulating agent affects MBCAT in a manner relevant to the beta-catenin pathway. In some cases, MBCAT modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MBCAT polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MBCAT activity, and hence the beta-catenin pathway. The MBCAT polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (*e.g.*, receptor-ligand binding), transcriptional activity (*e.g.*, using a reporter gene), enzymatic activity (*e.g.*, via a property of the substrate), activity of second messengers, immunogenicty and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MBCAT and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity

and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MBCAT-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MBCAT protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MBCAT-specific binding agents to function as negative effectors in MBCAT-expressing cells), binding equilibrium constants (usually at least about 10^7 M^{-1}, preferably at least about 10^8 M^{-1}, more preferably at least about 10^9 M^{-1}), and immunogenicity (e.g. ability to elicit MBCAT specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MBCAT polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MBCAT polypeptide can be full length or a fragment thereof that retains functional MBCAT activity. The MBCAT polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MBCAT polypeptide is preferably human MBCAT, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MBCAT interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MBCAT –specific binding activity, and can be used to assess normal MBCAT gene function.

Suitable assay formats that may be adapted to screen for MBCAT modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA, Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (*e.g.*, Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MBCAT and beta-catenin pathway modulators (e.g. U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); WO 01/25487 (Helicase assays), U.S. Pat. No. 6,114,132 (phosphatase and protease assays), U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Protein phosophatases catalyze the removal of a gamma phosphate from a serine, threonine or tyrosine residue in a protein substrate. Since phosphatases act in opposition to kinases, appropriate assays measure the same parameters as kinase assays. In one example, the dephosphorylation of a fluorescently labeled peptide substrate allows trypsin cleavage of the substrate, which in turn renders the cleaved substrate significantly more fluorescent (Nishikata M *et al.*, Biochem J (1999) 343:35-391). In another example, fluorescence polarization (FP), a solution-based, homogeneous technique requiring no immobilization or separation of reaction components, is used to develop high throughput screening (HTS) assays for protein phosphatases. This assay uses direct binding of the phosphatase with the target, and increasing concentrations of target- phosphatase increase the rate of dephosphorylation, leading to a change in polarization (Parker GJ et al., (2000) J Biomol Screen 5:77-88).

Proteases are enzymes that cleave protein substrates at specific sites. Exemplary assays detect the alterations in the spectral properties of an artificial substrate that occur upon protease-mediated cleavage. In one example, synthetic caspase substrates containing four amino acid proteolysis recognition sequences, separating two different fluorescent tags are employed; fluorescence resonance energy transfer detects the proximity of these fluorophores, which indicates whether the substrate is cleaved (Mahajan NP *et al.*, Chem Biol (1999) 6:401-409).

Polymerases catalyze the extension of newly synthesized DNA or RNA chains. Their activity may be monitored in an assay that uses labeled nucleotide analogs. For instance, a colorimetric polymerase assay monitors RNA synthesis using labeled ATP and GTP (Vassiliou W *et al.*, Virology (2000) 274:429-437).

Apoptosis assays. Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further

be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). Other cell-based apoptosis assays include the caspase-3/7 assay and the cell death nucleosome ELISA assay. The caspase 3/7 assay is based on the activation of the caspase cleavage activity as part of a cascade of events that occur during programmed cell death in many apoptotic pathways. In the caspase 3/7 assay (commercially available Apo-ONE™ Homogeneous Caspase-3/7 assay from Promega, cat# 67790), lysis buffer and caspase substrate are mixed and added to cells. The caspase substrate becomes fluorescent when cleaved by active caspase 3/7. The nucleosome ELISA assay is a general cell death assay known to those skilled in the art, and available commercially (Roche, Cat# 1774425). This assay is a quantitative sandwich-enzyme-immunoassay which uses monoclonal antibodies directed against DNA and histones respectively, thus specifically determining amount of mono- and oligonucleosomes in the cytoplasmic fraction of cell lysates. Mono and oligonucleosomes are enriched in the cytoplasm during apoptosis due to the fact that DNA fragmentation occurs several hours before the plasma membrane breaks down, allowing for accumalation in the cytoplasm. Nucleosomes are not present in the cytoplasmic fraction of cells that are not undergoing apoptosis. An apoptosis assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MBCAT function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MBCAT plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et*

al., 1986, Int. J. Cancer 38, 369; Campana *et al.*, 1988, J. Immunol. Meth. 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specfic to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee,D.N. 1995, J. Biol. Chem 270:20098-105). Cell Proliferation may also be examined using [^{3}H]-thymidine incorporation (Chen, J., 1996, Oncogene 13:1395-403; Jeoung, J., 1995, J. Biol. Chem. 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [^{3}H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL et al., 1998, In Vitro Cell Dev Biol Anim 34:239-46). Yet another proliferation assay, the MTS assay, is based on in vitro cytotoxicity assessment of industrial chemicals, and uses the soluble tetrazolium salt, MTS. MTS assays are commercially available, for example, the Promega CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Cat.# G5421).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook et al., Molecular Cloning, Cold Spring Harbor (1989)). For example, cells transformed with MBCAT are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Cell proliferation may also be assayed by measuring ATP levels as indicator of metabolically active cells. Such assays are commercially available, for example Cell Titer-Glo™, which is a luminescent homogeneous assay available from Promega.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW et al. (1986) Int J Radiat Biol Relat Stud Phys Chem Med 49:237-55). Cells transfected with an MBCAT may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent

can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MBCAT function plays a direct role in cell proliferation or cell cycle. For example, a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MBCAT plays a direct role in cell proliferation or cell cycle.

Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MBCAT function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MBCAT plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in

vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glyolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MBCAT in hypoxic conditions (such as with 0.1% O2, 5% CO2, and balance N2, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For example, a hypoxic induction assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MBCAT function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MBCAT plays a direct role in hypoxic induction.

Cell adhesion. Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells

expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include Matrigel™ (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-alpa. Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing an MBCAT's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic

signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MBCAT's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

Sprouting assay. A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900μl of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100 μl of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting

intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

Primary assays for antibody modulators

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MBCAT protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999, *supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MBCAT-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MBCAT gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MBCAT expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MBCAT) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MBCAT mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, *eds.*, John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MBCAT protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MBCAT mRNA expression, may also be used to test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MBCAT-modulating agent identified by any of the above methods to confirm that the modulating agent affects MBCAT in a manner relevant to the beta-catenin pathway. As used herein, MBCAT-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MBCAT.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MBCAT) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MBCAT–modulating agent results in changes in the beta-catenin pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use "sensitized genetic backgrounds", which, as used herein, describe cells or animals engineered for altered expression of genes in the beta-catenin or interacting pathways.

Cell-based assays

Cell based assays may detect endogenous beta-catenin pathway activity or may rely on recombinant expression of beta-catenin pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

Animal Assays

A variety of non-human animal models of normal or defective beta-catenin pathway may be used to test candidate MBCAT modulators. Models for defective beta-catenin pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the beta-catenin pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, beta-catenin pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal beta-catenin are used to test the candidate modulator's affect on MBCAT in

Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents, such as bFGF and VEGF, or with human tumor cells which over-express the MBCAT. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MBCAT is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, Oncogene 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MBCAT endogenously are injected in the flank, 1 x 10^5 to 1 x 10^7 cells per mouse in a volume of 100 µL using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde, 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorogenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate

period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorogenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorogenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorogenicity and modulator efficacy can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

Diagnostic and therapeutic uses

Specific MBCAT-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the beta-catenin pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the beta-catenin pathway in a cell, preferably a cell pre-determined to have defective or impaired beta-catenin function (e.g. due to overexpression, underexpression, or misexpression of beta-catenin, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MBCAT activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the beta-catenin function is

restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored beta-catenin function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for treating disorders or disease associated with impaired beta-catenin function by administering a therapeutically effective amount of an MBCAT -modulating agent that modulates the beta-catenin pathway. The invention further provides methods for modulating MBCAT function in a cell, preferably a cell pre-determined to have defective or impaired MBCAT function, by administering an MBCAT -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MBCAT function by administering a therapeutically effective amount of an MBCAT -modulating agent.

The discovery that MBCAT is implicated in beta-catenin pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and disorders involving defects in the beta-catenin pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MBCAT expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, *eds.*, John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective beta-catenin signaling that express an MBCAT, are identified as amenable to treatment with an MBCAT modulating agent. In a preferred application, the beta-catenin defective tissue overexpresses an MBCAT relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MBCAT cDNA sequences as probes, can determine whether particular tumors express or overexpress MBCAT. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MBCAT expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MBCAT oligonucleotides, and antibodies directed against an MBCAT, as described above for: (1) the detection of the presence of MBCAT gene

mutations, or the detection of either over- or under-expression of MBCAT mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MBCAT gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MBCAT.

Kits for detecting expression of MBCAT in various samples, comprising at least one antibody specific to MBCAT, all reagents and/or devices suitable for the detection of antibodies, the immobilization of antibodies, and the like, and instructions for using such kits in diagnosis or therapy are also provided.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MBCAT expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MBCAT expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer. The probe may be either DNA or protein, including an antibody.

EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. Drosophila beta-catenin screen

Two dominant loss of function screens were carried out in *Drosophila* to identify genes that interact with the Wg cell signaling molecule, beta –catenin (Riggleman et al. (1990) Cell 63:549-560; Peifer et al. (1991) Development 111:1029-1043). Late stage activation of the pathway in the developing *Drosophila* eye leads to apoptosis (Freeman and Bienz (2001) EMBO reports 2: 157-162), whereas early stage activation leads to an overgrowth phenotype. We discovered that ectopic expression of the activated protein in the wing results in changes of cell fate into ectopic bristles and wing veins.

Each transgene was carried in a separate fly stock:

Stocks and genotypes were as follows:

eye overgrowth transgene: isow; P{3.5 eyeless-Gal4}; P{arm(S56F)-pExp-UAS)}/TM6b;

eye apoptosis transgene: y w; P{arm(S56F)-pExp-GMR}/CyO; and

wing transgene: P{arm(ΔN)-pExp-VgMQ}/FM7c

In the first dominant loss of function screen, females of each of these three transgenes were crossed to a collection of males containing genomic deficiencies. Resulting progeny containing the transgene and the deficiency were then scored for the effect of the deficiency on the eye apoptosis, eye overgrowth, and wing phenotypes, i.e., whether the deficiency enhanced, suppressed, or had no effect on their respective phenotypes. All data was recorded and all modifiers were retested with a repeat of the original cross. Modifying deficiencies of the phenotypes were then prioritized according to how they modified each of the three phenotypes.

Transposons contained within the prioritized deficiencies were then screened as described. Females of each of the three transgenes were crossed to a collection of 4 types of transposons (3 piggyBac-based and 1 P-element-based). The resulting progeny containing the transgene and the transposon were scored for the effect of the transposon on their respective phenotypes. All data was recorded and all modifiers were retested with a repeat of the original cross. Modifiers of the phenotypes were identified as either members of the Wg pathway, components of apoptotic related pathways, components of cell cycle related pathways, or cell adhesion related proteins.

In the second dominant loss of function screen, females of the eye overgrowth transgene were crossed to males from a collection of 3 types of piggyBac-based transposons. The resulting progeny containing the transgene and the transposon were scored for the effect of the transposon on the eye overgrowth phenotype. All data was recorded and all modifiers were retested with a repeat of the original cross. Modifiers of the phenotypes were identified as either members of the Wg pathway, components of cell cycle related pathways, or cell adhesion related proteins.

II. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MBCAT symbol", and "MBCAT name aliases " provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MBCAT RefSeq_NA or GI_NA", "MBCAT GI_AA", "MBCAT NAME", and "MBCAT Description" provide the reference DNA sequences for the MBCATs as available from National Center for Biology Information (NCBI), MBCAT protein Genbank identifier number (GI#), MBCAT name, and MBCAT description, all available from Genbank, respectively. The length of each amino acid is in the "MBCAT Protein Length" column.

Names and Protein sequences of *Drosophila* modifiers of beta-catenin from screen (Example I), are represented in the "Modifier Name" and "Modifier GI_AA" column by GI#, respectively.

Table 1

MBCAT symbol	MBCAT name aliases	MBCAT RefSeq_NA or GI_NA	NA SEQ ID NO:	MBCAT GI_AA or RefSeq_AA	AA SEQ ID NO:	MBCAT name	MBCAT description	MBCAT protein length	Modifier name	Modifier GI_AA
POLR2E	POLR2E | RPB5 | XAP4 | RPABC1 | hRPB25 | hsRPB5 | DNA directed RNA polymerase II 23 kda polypeptide | polymerase (RNA) II (DNA directed) polypeptide E (25kD) | polymerase (RNA) II (DNA directed) polypeptide E, 25kDa	NM_002695	1	14589951	28	polymerase (RNA) II (DNA directed) polypeptide E, 25kDa	protein binding; DNA-directed RNA polymerase III; DNA-directed RNA polymerase II; DNA-directed RNA polymerase I	210	Rpb5	17945808
PPP1R3B	PPP1R3B | GL | PPP1R4 | FLJ14005 | protein phosphatase 1, regulatory (inhibitor) subunit 3B	NM_024607	2	13375815	29	protein phosphatase 1, regulatory (inhibitor) subunit 3B	protein phosphatase type 1, regulator; enzyme activator; protein binding; protein phosphatase 1 binding; protein phosphatase	285	CG9238	24664201

PPP1R3C	PPP1R3C | PPP1R5 | Phosphatase 1, regulatory inhibitor subunit 5 | protein phosphatase 1, regulatory (inhibitor) subunit 3C	NM_005398	3	4885559	30	protein phosphatase 1, regulatory (inhibitor) subunit 3C	protein phosphatase type 1, regulator; protein phosphatase 1 binding; protein phosphatase type 1	317	CG9238	24664201
LOC135264	LOC135264 | similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] | na	XM_069258	4	17463746	31	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	118	RpS12	24663646
LOC201829	LOC201829 | similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] | na	XM_116207	5	20471875	32	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	115	RpS12	24663646
LOC221147	LOC221147 | similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] | na	XM_169335	6	20548341	33	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	110	RpS12	24663646
LOC253068	LOC253068 | similar to 40S ribosomal protein S12 | na	XM_171698	7	22055843	34	similar to 40S ribosomal protein S12	na	96	RpS12	24663646

LOC283210	LOC283210 | similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] | na	XM_208564	8	27485488	35	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	132	RpS12	24663646
RPS12	RPS12 | 40S ribosomal protein S12 | ribosomal protein S12	NM_001016	9	14277700	36	ribosomal protein S12	RNA binding; structural constituent of ribosome	132	RpS12	24663646
C20orf13	C20orf13 | FLJ20212 | dJ585I14.2 | chromosome 20 open reading frame 13	NM_017714	10	8923202	37	chromosome 20 open reading frame 13	asparaginase	420	CG5241	21357893
MADH6	MADH6 | MADH7 | SMAD6 | Mothers against decapentaplegic, drosophila, homolog of, 6 | MAD (mothers against decapentaplegic, Drosophila) homolog 6 | MAD, mothers against decapentaplegic homolog 6 (Drosophila)	NM_005585	11	19923323	38	MAD, mothers against decapentaplegic homolog 6 (Drosophila)	protein binding; protein binding; receptor signaling protein serine/threonine kinase signaling protein; signal transducer; TGFbeta receptor, cytoplasmic mediator	496	Dad	17137382

MADH7	MADH7 | MADH8 | SMAD7 | Mothers against decapenta plegic, drosophila, homolog of, 7 | MAD (mothers against decapenta plegic, Drosophila) homolog 7 | MAD, mothers against decapenta plegic homolog 7 (Drosophila)	NM_005904	12	5174517	39	MAD, mothers against decapenta plegic homolog 7 (Drosophila)	apoptosis activator; protein binding; receptor signaling protein serine/threonine kinase signaling protein; TGFbeta receptor, inhibitory cytoplasmic mediator; TGFbeta receptor, cytoplasmic mediator; TGFbeta receptor, cytoplasmic mediator	426	Dad	17137382
DUSP1	DUSP1 | HVH1 | CL100 | MKP-1 | PTPN10 | serine/threonine specific protein phosphatase | dual specificity phosphatase 1	NM_004417	13	4758204	40	dual specificity phosphatase 1	protein kinase inhibitor; protein kinase inhibitor; non-membrane spanning protein tyrosine phosphatase; MAP kinase phosphatase; MAP kinase phosphatase	367	Mkp3	16648492
DUSP2	DUSP2 | PAC1 | PAC-1 | Dual-specificity phosphatase 2 | serine/threonine specific protein phosphatase | dual specificity phosphatase 2	NM_004418	14	4758206	41	dual specificity phosphatase 2	protein tyrosine phosphatase; protein tyrosine/threonine phosphatase	314	Mkp3	16648492

DUSP5	DUSP5 | HVH3 | VH1-like phosphatase 3 | serine/threonine specific protein phosphatase | dual specificity phosphatase 5	NM_004419	15	12707566	42	dual specificity phosphatase 5	protein tyrosine phosphatase; MAP kinase phosphatase	384	Mkp3	16648492
DUSP6	DUSP6 | MKP3 | MKP-3 | PYST1 | MAP kinase phosphatase 3 | serine/threonine specific protein phosphatase | dual specificity phosphatase 6	NM_001946 |NM_022652	16	4503419	43	dual specificity phosphatase 6	protein phosphatase; protein phosphatase; protein tyrosine/threonine phosphatase; MAP kinase phosphatase	381	Mkp3	16648492
DUSP7	DUSP7 | MKPX | MKP-X | PYST2 | Dual-specificity phosphatase-7 | dual specificity phosphatase 7	XM_037430	17	27481087	44	dual specificity phosphatase 7	protein binding; protein phosphatase; JUN kinase phosphatase; MAP kinase phosphatase	419	Mkp3	16648492
DUSP8	DUSP8 | HB5 | HVH8 | HVH-5 | H1 phosphatase, vaccinia virus homolog | serine/threonine specific protein phosphatase | dual specificity phosphata	NM_004420	18	4758212	45	dual specificity phosphatase 8	protein tyrosine phosphatase	625	Mkp3	16648492

	se 8									
DUSP9	DUSP9 | MKP4 | MKP-4 | map kinase phosphatase 4 | serine/threonine specific protein phosphatase | dual specificity phosphatase 9	NM_001395	19	4503421	46	dual specificity phosphatase 9	protein kinase inhibitor; protein phosphatase	384	Mkp3	16648492
DUSP4	DUSP4 | 1 | TYP | HVH2 | MKP2 | MKP-2 | MAP kinase phosphatase 2 | VH1 homologous phosphatase 2 | serine/threonine specific protein phosphatase | dual specificity phosphatase 4	NM_001394 |NM_057158	20	6808068	47	dual specificity phosphatase 4	protein binding; protein serine/threonine phosphatase; protein serine/threonine phosphatase; protein tyrosine/threonine phosphatase	303	Mkp3	16648492
LOC83693	LOC83693 | steroid dehydrogenase-like	NM_031463	21	24432037	48	steroid dehydrogenase-like	metabolism; metabolism; sex determination; development; development	330	CG31810	22946680
7h3	7h3 | FLJ13511 | hypothetical protein FLJ13511	NM_033025	22	24432043	49	hypothetical protein FLJ13511	Rho protein signal transduction	668	RhoGAP100F	73021070
MGC33637	MGC33637 | hypothetical protein MGC33637	NM_152596	23	22749225	50	hypothetical protein MGC33637	na	475	egl	21626660

SCAP	SCAP | KIAA0199 | SREBP CLEAVAGE-ACTIVATING PROTEIN	NM_012235	24	30923298	51	SREBP CLEAVAGE-ACTIVATING PROTEIN	na	1278	SCAP	28573975
LOC254700	LOC254700 | similar to Ubiquitin carboxyl-terminal hydrolase 12 (Ubiquitin thiolesterase 12) (Ubiquitin-specific processing protease 12) (Deubiquitinating enzyme 12) (Ubiquitin hydrolyzing enzyme 1) | na	XM_171244	25	22058861	52	similar to Ubiquitin carboxyl-terminal hydrolase 12 (Ubiquitin thiolesterase 12) (Ubiquitin-specific processing protease 12) (Deubiquitinating enzyme 12) (Ubiquitin hydrolyzing enzyme 1)	na	123	CG7023	7300926
USP12	USP12 | UBH1 | ubiquitin hydrolysing enzyme 1 | ubiquitin specific protease 12	19913513	26	19913514	53	ubiquitin specific protease 12	protein deubiquitination	370	CG7023	7300926
SPPL2A	SPPL2A | FLJ14540 | putative intramembrane cleaving protease | PSL2 | presenilin-like protein 2 | IMP3 | intramembrane protease 3	NM_032802	27	21314755	54	putative intramembrane cleaving protease	na	520	CG17370	7301394

III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MBCAT peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MBCAT activity.

IV. High-Throughput In Vitro Binding Assay.

^{33}P-labeled MBCAT peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM $MgCl_2$, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate beta-catenin modulating agents.

V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MBCAT proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at 15,000 × g for 15 min. The cell lysate is incubated with 25 μl of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase

coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VI. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues are obtained from Impath, UC Davis, Clontech, Stratagene, Ardais, Genome Collaborative, and Ambion.

TaqMan® analysis is used to assess expression levels of the disclosed genes in various samples.

RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. Single stranded cDNA is then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan® assay (Applied Biosystems, Foster City, CA) are prepared according to the TaqMan® protocols, and the following criteria: a) primer pairs are designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis is performed using a 7900HT instrument.

TaqMan® reactions are carried out following manufacturer's protocols, in 25 μl total volume for 96-well plates and 10 μl total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis is prepared using a universal pool of human cDNA samples, which is a mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data are normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples are compared with matched normal tissues from the same patient. A gene is considered overexpressed in a tumor when the level of expression of the gene is 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue is not available, a universal pool of cDNA samples is used instead. In these cases, a gene is considered overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type is greater than 2 times the

standard deviation of all normal samples (i.e., Tumor – average(all normal samples) > 2 x STDEV(all normal samples)).

A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other available detection method.

WHAT IS CLAIMED IS:

1. A method of identifying a candidate beta-catenin pathway modulating agent, said method comprising the steps of:

(a) providing an assay system comprising a MBCAT polypeptide or nucleic acid;

(b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and

(c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate beta-catenin pathway modulating agent.

2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MBCAT polypeptide.

3. The method of Claim 2 wherein the cultured cells additionally have defective beta-catenin function.

4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MBCAT polypeptide, and the candidate test agent is a small molecule modulator.

5. The method of Claim 4 wherein the assay is a binding assay.

6. The method of Claim 1 wherein the assay system is selected from the group consisting of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.

7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MBCAT polypeptide and the candidate test agent is an antibody.

8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MBCAT nucleic acid and the candidate test agent is a nucleic acid modulator.

9. The method of Claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.

11. The method of Claim 1 additionally comprising:

(d) administering the candidate beta-catenin pathway modulating agent identified in (c) to a model system comprising cells defective in beta-catenin function and, detecting a phenotypic change in the model system that indicates that the beta-catenin function is restored.

12. The method of Claim 11 wherein the model system is a mouse model with defective beta-catenin function.

13. A method for modulating a beta-catenin pathway of a cell comprising contacting a cell defective in beta-catenin function with a candidate modulator that specifically binds to a MBCAT polypeptide, whereby beta-catenin function is restored.

14. The method of Claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in beta-catenin function.

15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.

16. The method of Claim 1, comprising the additional steps of:

(e) providing a secondary assay system comprising cultured cells or a non-human animal expressing MBCAT ,

(f) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and

(g) detecting an agent-biased activity of the second assay system,

wherein a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived therefrom as a candidate beta-catenin pathway modulating agent,

and wherein the second assay detects an agent-biased change in the beta-catenin pathway.

17. The method of Claim 16 wherein the secondary assay system comprises cultured cells.

18. The method of Claim 16 wherein the secondary assay system comprises a non-human animal.

19. The method of Claim 18 wherein the non-human animal mis-expresses a beta-catenin pathway gene.

20. A method of modulating beta-catenin pathway in a mammalian cell comprising contacting the cell with an agent that specifically binds a MBCAT polypeptide or nucleic acid.

21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with the beta-catenin pathway.

22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.

23. A method for diagnosing a disease in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with a probe for MBCAT expression;

(c) comparing results from step (b) with a control;

(d) determining whether step (c) indicates a likelihood of disease.

24. The method of Claim 23 wherein said disease is cancer.

SEQUENCE LISTING

<110> EXELIXIS, INC.

<120> MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

<130> EX04-014C-PC

<150> US 60/454,469
<151> 2003-03-13

<150> US 60/470,728
<151> 2003-05-14

<150> US 60/479,795
<151> 2003-06-19

<150> US 60/479,769
<151> 2003-06-19

<160> 54

<170> PatentIn version 3.2

<210> 1
<211> 1238
<212> DNA
<213> Homo sapiens

<400> 1
ggcggcggcg gcggaggctg ccatggacga cgaggaggag acgtaccggc tctggaaaat 60

ccgcaagacc atcatgcagc tgtgccacga ccgtggctat ctggtgaccc aggacgagct 120

tgaccagacc ctggaggagt tcaaagccca atttggggac aagccgagtg aggggcggcc 180

gcggcgcacg gacctcaccg tgctggtggc ccacaacgat gaccccaccg accagatgtt 240

tgtgttcttt ccagaggagc ccaaggtggg catcaagacc atcaaggtgt actgccagcg 300

catgcaggag gagaacatca cacgggctct catcgtggtg cagcagggca tgacaccctc 360

cgccaagcag tccctggtcg acatggcccc caagtacatc ctggagcagt ttctgcagca 420

ggagctgctc atcaacatca cggagcacga gctagtccct gagcacgtcg tcatgaccaa 480

ggaggaggtg acagagctgc tggcccgata taagctccga gagaaccagc tgcccaggat 540

ccaggcgggg gaccctgtgg cgcgctactt tgggataaag cgtgggcagg tggtgaagat 600

catccggccc agtgagacgg ctggcaggta catcacctac cggctggtgc agtagctacc 660

gcctgacagc ccctagaggc ggacacacag cgacccccat ccctgcagga caaacgcccc 720

tgccctgcca gaatccggcc cccacagctc tcacggctgc tgctcctctg gactccccaa 780

ggcaggtggc ctccacccac gttctcccgt cctggggtga ggcttcctgt ggcccagccc 840

gccccattca cctgtggatt tgtgcgagat gcagcctcag aaggaacaag gcccccagag 900

ggaggtcacc tgggggcagc tggtgccggg tcttcaccca gaccacgctg ggtcccctct 960

gttgggggtt tggggtccgg gtctcccacc agccactgct tcctcctggg ccctcggctt 1020

ccacccctcg tcttccctcc ctcggggccc tgatgcgtgg cggcccccac ccggcctcgg 1080

ctctttactc cattcacagc catgcacgcg ctcaagtaca ccagggtgcg agatgccagc 1140

tctggagttc tcggttgttg taggaggttg ggtgttttca aatggtaaag atgttttgac 1200

gaaataaatt tgcttgatac agaaaaaaaa aaaaaaaa 1238

<210> 2
<211> 3807
<212> DNA
<213> Homo sapiens

<400> 2
gacatctccg ggaacccagc ccaggccctg cctcccggac acaccgacgc tcacgtagtc 60

gcgcttgcca caaccctgcg ggctctccga tgcggcgagc gagctgggga gggggcttct 120

ccgcggccca aaagcctgtt catctagccc catgatggct gtggacatcg agtacagata 180

caactgcatg gctccttcct tgcgccaaga gaggtttgcc tttaagatct caccaaagcc 240

cagcaaacca ctgaggcctt gtattcagct gagcagcaag aatgaagcca gtggaatggt 300

ggccccggct gtccaggaga agaaggtgaa aaagcgggtg tccttcgcag acaaccaggg 360

gctggccctg acaatggtca aagtgttctc ggaattcgat gacccgctag atatgccatt 420

caacatcacc gagctcctag acaacattgt gagcttgacg acagcagaga gcgagagctt 480

tgttctggat ttttcccagc cctctgcaga ttacttagac tttagaaatc gacttcaggc 540

cgaccacgtc tgccttgaga actgtgtgct caaggacaag gccattgcag gcactgcgaa 600

ggttcagaac ctcgcatttg agaagaccgt gaaaataagg atgacgttcg acacctggaa 660

gagctacaca gactttcctt gtcagtacgt gaaggacact tatgccggtt cagacaggga 720

cacgttctcc ttcgacatca gtttgcccga gaagattcag tcttatgaaa gaatggagtt 780

tgctgtgtac tacgagtgca atggacagac gtactgggac agcaacagag gcaagaacta 840

taggatcatc cgggctgagt taaaatctac ccagggaatg accaagcccc acagtggacc 900

ggatttggga atatcctttg accagttcgg aagccctcgg tgttcctatg gtctgtttcc 960

agagtggcca agttacttag gatatgaaaa gctagggccc tactactagt gactgcaggt 1020

gacagggcgt ggcggagctg ccacagacaa gcctagctct gctcactgtg cagtggagat 1080

ggaaggccag ggaggagcaa cgtggaactt ccatgaggcc ccgtttggga aaataaaagg 1140

atcctcttca cttctttctt aaacagcaaa tccagccagg ttcagattac acaaccagtg 1200

tctcactcaa aggagcagtg gtggctggcg cgctttcgca ctgtggcagc cacgagagtc 1260

tgtgcacgtc tgtgctggaa agggtatgga tgggaatcaa gcctatgcca gtgctgatga 1320

agctggagga gtctctcttc tgctctccac tcagatgtgg gacatcagtc gccaaaagcc 1380

actcagcccc agccacctcg cgtgagaccc tcactgttca ttgtgttcat ctttgggtgc 1440

tctctgccag ccaggccttt cctgcaagct gctgtgcttc cccgtccacg tgtatctctg 1500

ctgtgacaca ctgagctgac gcacatctcc agtgcagctg cagaagagaa atgggattgg 1560

ctcttgtttt ctgcaagttc atgttttgca ttttatgttc ttccacaatt gatctgatgt 1620

tcaggaaaag ataataaagg caaattagtt agtggttgag acaggcattt cctcctcccg 1680

cttcttgacc ccacagatgt attccagcag agagcaacac accagtcatc aaaacccact 1740

ggctcctgtg cggtgtcaca gattgcaggg ttctgacaag gcaggacagt caagagtggg 1800

gacactttca gcttctactt ttgccttcta gggggagctt tctaagtccc cacatttacc 1860

ccgagtcacc ggaaaaatct gatttttccc ccgaaagctc aatgacttta acgtgcttgg 1920

ctggtttgtc tcattcttta tgaaagaatt ttggggccgg gcgcggtggc ttatgcctgt 1980

aatcccagca ctttgggagg ccgaggcagg tggatcacga ggtcaggaga tcgagaccat 2040

cctggctaac acggtgaaac cctgtctcta ctaaaaatac aaaaaaatta gccaggcgtg 2100

gtggcgggcg cctgtagtcc cagctacttg ggaggctgag gcaggagaat ggcgggaacc 2160

tgggaggcgg agcttacagt gaaccgagat cacaccactg cattcccgcc tgggcagcag 2220

agcgagactc cgtctcaaac agaaaaaaaa agagaatttt gaatctcctt tcccaaagag 2280

tcatcttttc tgctgtgttt aggacatttg atttgcatat ccaatatctc ctcgaaacct 2340

tcagaaaatg gttttatcgt gactgtgatt cacactatct agaacacttt accagcaccc 2400

agggacatgg acttgggtgt tcttatttat ggtgtgtatg taaagagata ggggagaaaa 2460

acctcaccca agttcttata cgttatttta aacgtttgcc aactctgaaa tttcagagat 2520

tcattgttct taaccatatt ggactaaagt ctgttggtta gtgctgttgt aaaagagacc 2580

tctggggccg agtgtggtgg cttatgcctg taatccctgc actttgggaa gccaaggcgg 2640

gcagctcacc tgaggtcagg cgttcaagac cagcctggcc aacatggtga aacctcgtct 2700

gtactaaaaa tacaaaattt agctgagtgt ggtggcaggc gcctgtaatc cagctactcg 2760

ggaggctgag gcaggagaat cacttgaacc caggaggtgg aggttgcagt gagccgagat 2820

cacgtcactg catttcagcc tgagcgacag agtgaaactg tctcaaaaaa gagagacttc 2880

cgggacagtc attatcagat aggccccaaa cctgtgattt ttcttgggca agattggtgt 2940

ttacttaggg gtgttttaaa aatatatttt tacaagtata cttgtaggaa gttggttttt 3000

tattttctat ttttgtttgt ttttggagtt tggttaaacg actcttttat tttctgtttt 3060

gccttatctt actaaagtga agttttccta aggcaagcaa gaagaggagt ggaagcacag 3120

ttgcctggat ttggaggcag agttgtcagg cttttcaagc taagagtctt gtgcttggat 3180

tttccagatt aatttgaaaa gacctcccat ttgtggcttt gtacataacc aacaggcaga 3240

tactgagtgc cttggctcct agagttttgt ggttgggtta ggttgttttt gttgttgttt 3300

tgttttggtt ttgttttcat ttctgaagtt taagatgcct tgacttttta aatgctctta 3360

aggctattcg atgtaattct tactcctaaa actggctgtt cttagcctga aatctaatgc 3420

tttgtttttt gtacctctcc caggtgggta acactctagg atgacatgat gttataattt 3480

taggggaaat cacattttta ccttatgctg ttactgggca gaaccacgtt ttatgtaaac 3540

ataccagaca tcgggtaaca gacagtactt taaatgttat aaatttggtg atcagaacta 3600

ttaatagcat aaatcgaact caaatggaag caaaactgat ttcatgcagg tcctgaattt 3660

tactttgcct taagaagtgc cctccccaca atgcaggaga ggcacagagt gcactgtcat 3720

tgacatgtta cccgactaag gatcactctg ttcataagaa aaaggcctga agtgactctg 3780

tttaataaag tcagtttaat tttatct 3807

<210> 3
<211> 2524
<212> DNA
<213> Homo sapiens

<400> 3
ggggaatttg tgcaggcagc gggtgctggc ttttagggtc cgccgcctct ctgcctaatg 60

agctgcacca gaatgatcca ggttttagat ccacgtcctt tgacaagttc ggtcatgccc 120

gtggatgtgg ccatgaggct ttgcttggca cattcaccac ctgtgaagag tttcctgggc 180

ccgtacgatg aatttcaacg acgacatttt gtgaataaat taaagcccct gaaatcatgt 240

ctcaatataa aacacaaagc caaatcacag aatgactgga agtgctcaca caaccaagcc 300

aagaagcgcg ttgtgtttgc tgactccaag ggcctctctc tcactgcgat ccatgtcttc 360

tccgacctcc cagaagaacc agcgtgggat ctgcagtttg atctcttgga ccttaatgat 420

atctcctctg ccttaaaaca ccacgaggag aaaaacttga ttttagattt ccctcagcct 480

tcaaccgatt acttaagttt ccggagccac tttcagaaga actttgtctg tctggagaac 540

tgctcattgc aagagcgaac agtgacaggg actgttaaag tcaaaaatgt gagttttgag 600

aagaaagttc agatccgtat cactttcgat tcttggaaaa actacactga cgtagactgt 660

gtctatatga aaaatgtgta tggtggcaca gatagtgata ccttctcatt tgccattgac 720

ttacccccctg tcattccaac tgagcagaaa attgagttct gcatttctta ccatgctaat 780

gggcaagtct tttgggacaa caatgatggt cagaattata gaattgttca tgttcaatgg 840

aagcctgatg gggtgcagac acagatggca ccccaggact gtgcattcca ccagacgtct 900

cctaagacag agttagagtc aacaatcttt ggcagtccga ggctggctag tgggctcttc 960

ccagagtggc agagctgggg gagaatggag aacttggcct cttatcgatg aattaagcaa 1020

caatgtaact ggtcttgact tgtcatattc ccccatgcaa tcctaggtct gtattgctca 1080

attttaggaa gcctttgcta ctccatcagt aggtttagat ttgagctttt gagacctggc 1140

tatggaaaag aaagacactt gagaatttag tgttggggtc tgtacagatg atgctaccca 1200

atttggcttt gaaggatcaa gtaacaggtt gaaaactatt tttataaagg taatactttt 1260

tcagttccct tcttccttcc ctctcaatcc actagctttc atgttgggca aggaaaagtt 1320

gaggaaggat ggctgatggt gatggaaagc tgtgttaatg gtatgaggaa tgtgtgaaaa 1380

gtatacacaa agggctctga agctcaagtc agaggagtgg gaggtctgat cattgttggt 1440

ggaaaaacgt aaggttattt tgtgttttta agttggtttt acaattcttt cctggggaaa 1500

ttatttctgg aggggaaaaa gatccattct acgtatcctt gtggagaaaa gctaaataac 1560

ctttaagaat gtgggtggta ttggagaaag aagatgaatt atagctccgg agaatcaaga 1620

tcttaagtga agcctttctg ttcagatgtg atctataaaa aatcataatt tggggaaagt 1680

ttaagcaaat ctggctttgt agtcctgatg ttataagtga ctttgtgatc aaactgtcag 1740

gcttgggttc ttgttataga atgcttggta tagaaaaacc atgccatcat taatggctaa 1800

caacacgtag ggacttcatg tcatgtcaaa gatagctctt tgcaagtgcc ttgattaaac 1860

cagaaaactg tcatcgttta acccaaatat ctgaatggtc atctggtaac tcatgggttt 1920

ttggcctcat aagatggtcc actctgtaca caggcattcc tcctgcaata atgttgtatc 1980

tttgagaccg ttgtcagtgt acacaactca catccttcat attgaaggtg actcattttt 2040

ctgcacactt ttttgatgtg atgcttgacg tgaggcccga cactaggatt ctcaatgcaa 2100

gaatccagta ccttgcacat agaagtagca acccatccct tgcctatttt catcttgctg 2160

ttttcttttt tttaaaaaaa tggatgtgac ttgttttgaa tgttttgtat tatacttgtt 2220

tttgtgtgtg cataaattca ttctgtagga tcttaagaaa aagagtccca gaatgttgct 2280

tctattattg tgcacaacca ttgagaggtg ttacgagaat gcagttaatt ttaacatgtg 2340

tgatgtgcca tggtggaaaa gtactatcgg aataactctg cagtgacaga atttgaagtt 2400

tggctagcat ccatactttt ctactgtaaa tatttcactc tcctctagct atccttgatg 2460

agcttctcac tttaagaata aatgtgtttg atacaaaaaa aaaaaaaaaa gaaaaaaaaa 2520

aaaa 2524

<210> 4
<211> 357
<212> DNA
<213> Homo sapiens

<400> 4
atggccaagg aaggcattgc tgctggaggt gtaatggacg ttaatactgc tttacaagag 60

gtgctgaaga ccgccctcat ccacgatggc ctagcacgtg gaattcacga agctgccgaa 120

gccttagaca agtgccaagc ccatcttttc gtggaggccc tttgccatga acaccaaatc 180

aacctaatta aggttgatga caacaagaaa ctaggggaaa ggataggcct ctgtaaaatt 240

aacagagaag ggaaaccctg taaagtggtt ggttgcagtt gtgtagtagt taaggactat 300

ggcaaggagt ctcaggccaa ggatgtcatc caagagtact tcaaatgcaa gaaatga 357

<210> 5
<211> 348
<212> DNA
<213> Homo sapiens

<400> 5
atggccgagg aaggcattac tgctggaggt ataatggaag ttaatactgc tttacaagaa 60

gtgctgaaga ccgccctcgt ccatgatggc ccagcatgtg gaattcttga agctgccaaa 120

gccttagaca agtgccaagc ccatctttgt gtgcttgcat ccaactgtga tgagcctgtg 180

tatgtcaagt tggtggaggc cttttgcgct gaacaccgaa ccaaccgact taagagaggg 240

gaaagtggtt gtaaagtggt tggtggcagt tgtgtagaag ttaaggacgc tggcaaggag 300

tgtcaggcca aggatgtcat caaagagtac ttcaaatgca agaaatga 348

<210> 6
<211> 333
<212> DNA
<213> Homo sapiens

<400> 6
atggccaagg aaggcattgc tgctggaggt gtaatggaca ttaatactgc tttacaagag 60

gtgctgaaga ccaccctcat ccacgatggc ctagcacgtg gaattcacga agctgccaaa 120

cccttagaca agggccaagc ccatctttat gtgcttgcat ccaactgtga tgagactgtg 180

tatgtcaagt tggtggaagc catttgtgct aaacaccaaa tcaacttcat taaggttgat 240

gacaacaaga aagtagggga atggttaagg actatggcaa ggaatctcag gccaaggatg 300

tccctcgaag agtacttcaa atgcaagaaa tga 333

<210> 7
<211> 291
<212> DNA
<213> Homo sapiens

<400> 7
atggcccagg aaggcatcag tgctggaggt gtcatggacc ttaatactgc tttacaagag 60

gtcctgaagg ctgccctcat ccatgatggc ctagcacgtg gaattcgaga agctgccaaa 120

gccttagaca agtgctgggc ccatccttgt gctgccccca actcctgcct atgtggctgg 180

ctggtgaagg cccttgttgc tgagcaccag atcaccctaa ttaaggttga tgacaataaa 240

ctaggggaag ggatggacca ctgtaaaact gacagaagga aaaccccata a 291

<210> 8
<211> 500
<212> DNA
<213> Homo sapiens

<400> 8
ctttccctcc tgccgccgag tcgcgcggag gcggaggctt gggtgcgttc aagattcagg 60

ttcacccgta acccactgcc atggccgagg aaggcattgc tgctggaggt gtaatggagg 120

ttaatactgc tttacaagag gtgctgaaga ccgccctcat ccacgatggc ctagcacgtg 180

gaattcgcga agctgccaaa gtcttagaca agcgccaagc ccatctttgt gtgcttgcat 240

ccaactgtga tgagcctatg tatgtcaagt tggtggaggc cctttgtgct gaacaccaaa 300

tcaacctaat taaggttgat gacaacaaga aactaggaga atgggtaggc ctctgtaaaa 360

ttgacagaga ggggaaaccc cataaagtgg ttggttacag ttgtgtagta gttaaggact 420

atggcaagga gtctcaggcc aaggatgtca tcgaagagta tttcaaatgc aagaaatgaa 480

gaaataaatc tttggctcac 500

<210> 9
<211> 534
<212> DNA
<213> Homo sapiens

<400> 9
ctttccctgc cgccgccgag tcgcgcggag gcggaggctt gggtgcgttc aagattcagc 60

ttcacccgta acccaccgcc atggccgagg aaggcattgc tgctggaggt gtaatggacg 120

ttaatactgc tttacaagag gttctgaaga ctgccctcat ccacgatggc ctagcacgtg 180

gaattcgcga agctgccaaa gccttagaca agcgccaagc ccatctttgt gtgcttgcat 240

ccaactgtga tgagcctatg tatgtcaagt tggtggaggc cctttgtgct gaacaccaaa 300

tcaacctaat taaggttgat gacaacaaga aactaggaga atgggtaggc ctttgtaaaa 360

ttgacagaga ggggaaaccc cgtaaagtgg ttggttgcag ttgtgtagta gttaaggact 420

atggcaagga gtctcaggcc aaggatgtca ttgaagagta tttcaaatgc aagaaatgaa 480

gaaataaatc tttggctcac aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 534

<210> 10
<211> 2347
<212> DNA
<213> Homo sapiens

<400> 10
gctgaagcgg ggtaattcct ctcctgcaat tacttttgga tggaagtatg ccccttctc 60

agtagaagat ggtaatcttg gagaatgacc atggagaagg ggatgagttc tggagaaggg 120

ctgccttcca gatcatctca ggtttcggct ggtaaaataa cagccaaaga gttggaaaca 180

aagcagtcct ataaagagaa acgaggaggc tttgtgttgg tgcatgcagg tgcaggttat 240

cattctgaat ccaaagccaa ggagtataaa catgtatgca aacgagcttg tcagaaggca 300

attgaaaagc tgcaggccgg tgctcttgca actgacgcag tcactgcagc actggtggaa 360

cttgaggatt ctccttttac aaatgcagga atgggatcta atctaaatct gttaggtgaa 420

attgagtgtg atgccagcat aatggatgga aaatccttaa attttggagc agttggagca 480

ctgagtggaa tcaagaaccc ggtctcggtt gccaacagac tcttatgtga agggcagaag 540

ggcaagctct cggctggcag aattcctccc tgctttttag ttggagaagg agcctacaga 600

tgggcagtag atcatggaat accctcttgc cctcctaaca tcatgaccac aagattcagt 660

ttagctgcat ttaaaagaaa caagaggaaa ctagagctgg cagaaagggt ggacacagat 720

tttatgcaac taaagaaaag aagacaatca agtgagaagg aaaatgactc aggcactttg 780

gacacggtag gcgctgtggt tgtggaccac gaagggaatg ttgctgctgc tgtctccagt 840

ggaggcttgg ccttgaaaca tccggggaga gttgggcagg ctgctcttta tggatgtggc 900

tgctgggctg aaaatactgg agctcataac ccctactcca cagctgtgag tacctcagga 960

tgtggagagc atcttgtgcg caccatactg gctagagaat gttcacatgc tttacaagct 1020

gaggatgctc accaagccct gttggagact atgcaaaaca agtttatcag ttcacctttc 1080

cttgccagtg aagatggcgt gcttggcgga gtgattgtcc tccgttcatg cagatgttct 1140

gccgagcctg acttctccca aaataagcag acacttctag tggaatttct gtggagccac 1200

acgacggaga gcatgtgtgt cggatatatg tcagcccagg atgggaaagc caagactcac 1260

atttcaagac ttcctcctgg tgcggtggca ggacagtctg tggcaatcga aggtggggtg 1320

tgccgcctgg agagcccagt gaactgaccc ttcaggctga gtgtgaagcg tctcagaggc 1380

atttcagaac ctgagctttt gggggttttt aactgaagtt ggttgtttta tctttcttgt 1440

tttataattc ctattgcaac ctcgtgcact gctcgagaca caagtgctgc tgtagttagc 1500

gcttagtgac acgcgggcct ttggtgggtg agcgggactg tgtgtgagtg tgtgcgcgta 1560

tgtgcgcaca tatgtgtatg tgtggagtat gtgtgtttgc ttctccgtgg atgaaataga 1620

aactcctcat tgtgtgacca ggaatggtta aatcatcttt acaaaatgtg tgctttaact 1680

gtttacaagt aaaacctaaa gttgcaggaa acatttttta tttcgtaaag aggtaccaac 1740

tgtcgctgat gtgatatgtc agaactgaag agtaaatcta cttgtttaaa tgacttgaca 1800

gtggtagtgc tccatttaat aacagtaata agtaataaag tgtttttatt tgttaaccag 1860

tttaagtgga tcctgtggta acttaaactg ttgttctcat cccttatatg gggcattttt 1920

ctttaacaaa gaatggtttc agtgaaacaa tctagcagag aattaatgtc agaacctttt 1980

taaataatag tctgattgat acagtttgta cttatttcat caagcttttc taagcttaaa 2040

tattgcatag cttcgagctg tatggactat attatgaaag aatatgtaaa gagaacatac 2100

agtaatgcac agtccttaat ttgtgtataa tggaaagtta tttacaatat aacactgtaa 2160

ataagaaagc aaagtttatg ggaaaattca atattatctt tgtttttgtt taaatatatt 2220

tttaagataa aggcacaaaa ataaaagaag cgtattactg ggtatagtat gtgactcctc 2280

ttctcagact aataaattat cttttgaatc cttggaaaaa aaaaaaaaaa aaaaaaaaaa 2340

aaaaaaa 2347

<210> 11
<211> 2887
<212> DNA
<213> Homo sapiens

<400> 11
gaattcggca cgaggagcga tcgagggagc tgagccgaga gaaagagccg ccgggcgctg 60

cctcgccaga cctcgctggg accccggggc caccgggagg cacttttgtg gaggggggag 120

gggggcgac ctcggcagcc tcggcgcacg aagcgtccga gggcagcgtg gggygggctg 180

cgacctctgc atcggtggac tgcattttta attaaggatt cccagcagct ctttgggatt 240

tttacagctt ccactcatgt gttgacaccc gcgtccagga gaaactcgct ccaagtgcat 300

ctagcgcctg ggacctgaga cggcgttggc ctttcgtgca tgcaaatcca gggatttagg 360

ttttgtttgg gatttccttt tctttctttc ctttttttt tctttttgca gggagtaaga 420

agggagctgg gggtatcaac aagcctgcct ttcggatcct gcgggaaaag cccatgtagt 480

taagcgcttt ggtttaaaaa aaaggcaagg taaaggcagg gctttccaga cacatttagg 540

ggttcgcgcg agctttgtgc tcatggacca gccgcacaac ttttgaaggc tcgccggccc 600

atgtggggtc tttctggcgg gccgcctgca gccccctaa agcgcggggg gctggagttg 660

ttgagcagcc ccgccgctgt ggtccatgta gccgctggcc gcgcgcggaa tgcggcttcg 720

cgtgcgcgtg ttcccggccg tcccgccttg gcgaggtccc tcatgttgtt gccctgcggc 780

gccccttga agacaggctg tgcgcggttt gcacggcggt ccgcggcgga ggttcatgtg 840

ggggtgcgac ccgcgcagcc ggcgccttgt tgagggaacg gacccccggt aaccggagac 900

cgcctccccc ccacccctgg cgccaaagga tattgtatgt tcaggtccaa acgctcgggg 960

ctggtgcggc gactttggcg aagtcgtgtg gtccccaacc gggaggaagg cggcagcggc 1020

ggcggcggtg gcggcgacga ggatgggagc ttgggcagcc gagctgagcc ggccccgcgg 1080

gcaagagagg gcggaggctg cggccgctcc gaagtccgcc cggtagcccc gcggcggccc 1140

cgggacgcag tgggacagcg aggcgcccag ggcgcgggga ggcgccggcg cgcaggggcc 1200

ccccccgaggc ccatgtcgga gccaggggcc ggcgctggga gctccctgct ggacgtggcg 1260

gagccgggag gcccgggctg gctgcccgag agtgactgcg agacggtgac ctgctgtctc 1320

ttttcggagc gggacgccgc cggcgcgccc cgggacgcca gcgacccccc ggccggggcg 1380

gccctggagc cggcgggcgg cgggcggagt cgcgaagcgc gctcgcggct gctgctgctg 1440

gagcaggaac tcaaaaccgt cacgtactcg ctgctgaagc ggctcaagga gcgctcgctg 1500

gacacgctgc tggaggcggt ggagtcccgc ggcggcgtgc cgggcggctg cgtgctggtg 1560

ccgcgcgccg acctccgcct gggcggccag cccgcgccgc cgcagctgct gctcggccgc 1620

ctctttcgct ggcccgacct gcagcacgcc gtggagctga agcccctgtg cggctgccac 1680

agcttcgccg ccgccgccga cggccctacc gtgtgctgca acccctacca cttcagccgg 1740

ctctgcgggc ccgaatctcc gccacctccc tactctcggc tgtctcctcg cgacgagtac 1800

aagccactgg atctgtccga ttccacattg tcttacactg aaacggaggc taccaactcc 1860

ctcatcactg ctccgggtga attctcagac gccagcatgt ctccggacgc caccaagccg 1920

agccactggt gcagcgtggc gtactgggag caccggacgc gcgtgggccg cctctatgcg 1980

gtgtacgacc aggccgtcag catcttctac gacctacctc agggcagcgg cttctgcctg 2040

ggccagctca acctggagca gcgcagcgag tcggtgcggc gaacgcgcag caagatcggc 2100

ttcggcatcc tgctcagcaa ggagcccgac ggcgtgtggg cctacaaccg cggcgagcac 2160

cccatcttcg tcaactcccc gacgctggac gcgcccggcg gccgcgccct ggtcgtgcgc 2220

aaggtgcccc ccggctactc catcaaggtg ttcgacttcg agcgctcggg cctgcagcac 2280

gcgcccgagc ccgacgccgc cgacggcccc tacgacccca acagcgtccg catcagcttc 2340

gccaagggct gggggccctg ctactcccgg cagttcatca cctcctgccc ctgctggctg 2400

gagatcctcc tcaacaaccc cagatagtgg cggccccggc gggaggggcg ggtgggaggc 2460

cgcggccacc gccacctgcc ggcctcgaga ggggccgatg cccagagaca cagcccccac 2520

ggacaaaacc ccccagatat catctaccta gatttaatat aaagttttat atattatatg 2580

gaaatatata ttatacttgt aattatggag tcatttttac aatgtaatta tttatgtatg 2640

gtgcaatgtg tgtatatgga caaaacaaga aagacgcact ttggcttata attctttcaa 2700

tacagatata ttttctttct cttcctcctt cctcttcctt acttttttata tatatatata 2760

aagaaaatga tacagcagag ctaggtggaa aagcctgggt ttggtgtatg gtttttgaga 2820

tattaatgcc cagacaaaaa gctaatacca gtcactcgat aataaagtat tcgcattata 2880

aaaaaga 2887

<210> 12
<211> 3111

<212> DNA
<213> Homo sapiens

<400> 12
ggcacgagcg gagagccgcg cagggcgcgg gccgcgcggg gtggggcagc cggagcgcag 60

gcccccgatc cccggcgggc gcccccgggc ccccgcgcgc gccccggcct ccgggagact 120

ggcgcatgcc acggagcgcc cctcgggccg ccgccgctcc tgcccgggcc cctgctgctg 180

ctgctgtcgc ctgcgcctgc tgccccaact cggcgcccga cttcttcatg gtgtgcggag 240

gtcatgttcg ctccttagca ggcaaacgac ttttctcctc gcctcctcgc cccgcatgtt 300

caggaccaaa cgatctgcgc tcgtccggcg tctctggagg agccgtgcgc ccggcggcga 360

ggacgaggag gagggcgcag ggggaggtgg aggaggaggc gagctgcggg gagaaggggc 420

gacggacagc cgagcgcatg gggccggtgg cggcggcccg ggcagggctg gatgctgcct 480

gggcaaggcg gtgcgaggtg ccaaaggtca ccaccatccc cacccgccag ccgcgggcgc 540

cggcgcggcc gggggcgccg aggcggatct gaaggcgctc acgcactcgg tgctcaagaa 600

actgaaggag cggcagctgg agctgctgct ccaggccgtg gagtcccgcg gcgggacgcg 660

caccgcgtgc ctcctgctgc ccggccgcct ggactgcagg ctgggcccgg gggcgcccgc 720

cggcgcgcag cctgcgcagc cgccctcgtc ctactcgctc cccctcctgc tgtgcaaagt 780

gttcaggtgg ccggatctca ggcattcctc ggaagtcaag aggctgtgtt gctgtgaatc 840

ttacgggaag atcaaccccg agctggtgtg ctgcaacccc catcacctta gccgactctg 900

cgaactagag tctccccccc ctccttactc cagatacccg atggattttc tcaaaccaac 960

tgcagactgt ccagatgctg tgccttcctc cgctgaaaca gggggaacga attatctggc 1020

ccctgggggg ctttcagatt cccaacttct tctggagcct ggggatcggt cacactggtg 1080

cgtggtggca tactgggagg agaagacgag agtggggagg ctctactgtg tccaggagcc 1140

ctctctggat atcttctatg atctacctca ggggaatggc ttttgcctcg gacagctcaa 1200

ttcggacaac aagagtcagc tggtgcagaa ggtgcggagc aaaatcggct gcggcatcca 1260

gctgacgcgg gaggtggatg gtgtgtgggt gtacaaccgc agcagttacc ccatcttcat 1320

caagtccgcc acactggaca acccggactc caggacgctg ttggtacaca aggtgttccc 1380

cggtttctcc atcaaggctt tcgactacga gaaggcgtac agcctgcagc ggcccaatga 1440

ccacgagttt atgcagcagc cgtggacggg ctttaccgtg cagatcagct ttgtgaaggg 1500

ctggggtcag tgctacaccc gccagttcat cagcagctgc ccgtgctggc tagaggtcat 1560

cttcaacagc cggtagccgc gtgcggaggg gacagagcgt gagctgagca ggccacactt 1620

caaactactt tgctgctaat attttcctcc tgagtgcttg cttttcatgc aaactctttg 1680

gtcgtttttt ttttgtttgt tggttggttt tcttcttctc gtcctcgttt gtgttctgtt 1740

ttgtttcgct ctttgagaaa tagcttatga aaagaattgt tgggggtttt tttggaagaa 1800

ggggcaggta tgatcggcag gacaccctga taggaagagg ggaagcagaa atccaagcac 1860

caccaaacac agtgtatgaa ggggggcggt catcatttca cttgtcagga gtgtgtgtga 1920

gtgtgagtgt gcggctgtgt gtgcacgcgt gtgcaggagc ggcagatggg gagacaacgt 1980

gctctttgtt ttgtgtctct tatggatgtc cccagcagag aggtttgcag tcccaagcgg 2040

tgtctctcct gccccttgga cacgctcagt ggggcagagg cagtacctgg gcaagctggc 2100

ggctggggtc ccagcagctg ccaggagcac ggctctgtcc ccagcctggg aaagcccctg 2160

cccctcctct ccctcatcaa ggacacgggc ctgtccacag gcttctgagc agcgagcctg 2220

ctagtggccg aaccagaacc aattattttc atccttgtct tattcccttc ctgccagccc 2280

ctgccattgt agcgtctttc ttttttggcc atctgctcct ggatctccct gagatgggct 2340

tcccaagggc tgccggggca gccccctcac agtattgctc acccagtgcc ctctcccctc 2400

agcctctccc ctgcctgccc tggtgacatc aggtttttcc cggacttaga aaaccagctc 2460

agcactgcct gctcccatcc tgtgtgttaa gctctgctat taggccagca agcggggatg 2520

tccctgggag ggacatgctt agcagtcccc ttccctccaa gaaggatttg gtccgtcata 2580

acccaaggta ccatcctagg ctgacaccta actcttcttt catttcttct acaactcata 2640

cactcgtatg atacttcgac actgttctta gctcaatgag catgtttaga ctttaacata 2700

agctattttt ctaactacaa aggtttaaat gaacaagaga agcattctca ttggaaattt 2760

agcattgtag tgctttgaga gagaaaggac tcctgaaaaa aaacctgaga tttattaaag 2820

aaaaaaatgt attttatgtt atatataaat atattattac ttgtaaatat aaagacgttt 2880

tataagcatc attatttatg tattgtgcaa tgtgtataaa caagaaaaat aaagaaaaga 2940

tgcactttgc tttaatataa atgcaaataa caaatgccaa attaaaaaag ataaacacaa 3000

gattggtgtt ttttcctatg ggtgttatca cctagctgaa tgtttttcta aaggagttta 3060

tgttccatta aacgattttt aaaatgtaca cttgaaaaaa aaaaaaaaaa a 3111

<210> 13
<211> 2015
<212> DNA
<213> Homo sapiens

<400> 13
tcgctgcgaa ggacatttgg gctgtgtgtg cgacgcgggt cggaggggca gtcgggggaa 60

ccgcgaagaa gccgaggagc ccggagcccc gcgtgacgct cctctctcag tccaaaagcg 120

gcttttggtt cggcgcagag agacccgggg gtctagcttt tcctcgaaaa gcgccgccct 180

gcccttggcc ccgagaacag acaaagagca ccgcagggcc gatcacgctg ggggcgctga 240

ggccggccat ggtcatggaa gtgggcaccc tggacgctgg aggcctgcgg gcgctgctgg 300

gggagcgagc ggcgcaatgc ctgctgctgg actgccgctc cttcttcgct ttcaacgccg 360

gccacatcgc cggctctgtc aacgtgcgct tcagcaccat cgtgcggcgc cgggccaagg 420

gcgccatggg cctggagcac atcgtgccca acgccgagct ccgcggccgc ctgctggccg 480

gcgcctacca cgccgtggtg ttgctggacg agcgcagcgc cgccctggac ggcgccaagc 540

gcgacggcac cctggccctg gcggccggcg cgctctgccg cgaggcgcgc gccgcgcaag 600

tcttcttcct caaaggagga tacgaagcgt tttcggcttc ctgcccggag ctgtgcagca 660

aacagtcgac ccccatgggg ctcagccttc ccctgagtac tagcgtccct gacagcgcgg 720

aatctgggtg cagttcctgc agtaccccac tctacgatca gggtggcccg gtggaaatcc 780

tgccctttct gtacctgggc agtgcgtatc acgcttcccg caaggacatg ctggatgcct 840

tgggcataac tgccttgatc aacgtctcag ccaattgtcc caaccatttt gagggtcact 900

accagtacaa gagcatccct gtggaggaca accacaaggc agacatcagc tcctggttca 960

acgaggccat tgacttcata gactccatca agaatgctgg aggaagggtg tttgtccact 1020

gccaggcagg catttcccgg tcagccacca tctgccttgc ttaccttatg aggactaatc 1080

gagtcaagct ggacgaggcc tttgagtttg tgaagcagag gcgaagcatc atctctccca 1140

acttcagctt catgggccag ctgctgcagt ttgagtccca ggtgctggct ccgcactgtt 1200

cggcagaggc tgggagcccc gccatggctg tgctcgaccg aggcacctcc accaccaccg 1260

tgttcaactt ccccgtctcc atccctgtcc actccacgaa cagtgcgctg agctaccttc 1320

agagccccat tacgacctct cccagctgct gaaaggccac gggaggtgag gctcttcaca 1380

tcccattggg actccatgct ccttgagagg agaaatgcaa taactctggg aggggctcga 1440

gagggctggt ccttatttat ttaacttcac ccgagttcct ctgggtttct aagcagttat 1500

ggtgatgact tagcgtcaag acatttgctg aactcagcac attcgggacc aatatatagt 1560

gggtacatca agtccatctg acaaaatggg gcagaagaga aaggactcag tgtgtgatcc 1620

ggtttctttt tgctcgcccc tgttttttgt agaatctctt catgcttgac atacctacca 1680

gtattattcc cgacgacaca tatacatatg agaatatacc ttatttattt ttgtgtaggt 1740

gtctgccttc acaaatgtca ttgtctactc ctagaagaac caaatacctc aatttttgtt 1800

tttgagtact gtactatcct gtaaatatat cttaagcagg tttgttttca gcactgatgg 1860

aaaataccag tgttgggttt ttttttagtt gccaacagtt gtatgtttgc tgattattta 1920

tgacctgaaa taatatattt cttcttctaa gaagacattt tgttacataa ggatgacttt 1980

tttatacaat ggaataaatt atggcatttc tattg 2015

<210> 14
<211> 1702

<212> DNA
<213> Homo sapiens

<400> 14
ggagtcgacc gctcgggcag cgcaccgcca cgagagcccg ggacgcggga aagaccgaaa 60

ggaagaggaa gaggcaccgg tggccatggg gctggaggcg gcgcgcgagc tggagtgcgc 120

ggcgctgggc acgctgctgc gggatccgcg ggaggcggaa cgcacgctgc tgctggactg 180

ccgccccttc ctggccttct gccggcgcca cgtgcgcgcc gcgcggccag tgccttggaa 240

cgcgctgctg cggcgccgcg cgcgcggccc tcctgccgcc gttctcgcct gcctgctgcc 300

cgaccgcgcg ctgcggacgc gcctggtccg cggggagctg gcgcgggccg tggtgctgga 360

cgagggcagt gcctcggtgg cggagctccg gcccgacagc ccggctcatg tgctgctggc 420

cgcgctgctg cacgagaccc gcgcggggcc cactgccgtg tacttcctgc gaggaggctt 480

cgacggcttc cagggctgct gtcccgatct gtgctctgag gcccccgccc ctgcgctgcc 540

gccaacaggg gacaaaacca gccgctccga ctccagggct cctgtctacg accagggtgg 600

ccctgtggag atcttgccct acctgttcct gggcagctgc agtcactcgt cagacctgca 660

ggggctgcag gcctgtggca tcacagccgt cctcaacgtg tccgccagct gccccaacca 720

ctttgagggc cttttccgct acaagagtat ccctgtggag gacaaccaga tggtggagat 780

cagtgcctgg ttccaggagg ccataggctt cattgactgg gtgaagaaca gcggaggccg 840

ggtgctggtg cactgccagg cgggtatctc gcgctctgcc accatctgtc tggcatacct 900

catgcagagt cgccgtgtgc ggctggacga ggcctttgac ttcgttaagc agcgccgggg 960

ggtcatctcc cccaacttca gtttcatggg gcagctgctg cagtttgaga cccaggtgct 1020

gtgtcactga ggtggtgccc ctctgcctgc ctgccccact gtgctggcag gagctgactg 1080

tggactggtg ggctcccctc tgggccagca cagtcccctc acctccggca gggctgctac 1140

ctcctcagag tttcagaagc ccccacatgg gggctctagg aatgccggca tgctggtctt 1200

tccgacctgg tgctcttctg ctgggggact gaggctggcc ctcattcggg gtcgggaacc 1260

aagggtgtgt ctgctctttc cctccccatc ctctggcaga aatcagctag acgctatacc 1320

gtggactctc cctggtccac caccatgttg aagcccttgg cagcctgaga gctccaagga 1380

acaagctgtg acaaccagga gccctgtctg tgggttcgtc tgcccagggc ctggagccca 1440

agccctgtgt tcctggggaa gctggggact tgggaagtga tgggtgtgtc atgttgcgtg 1500

tgtctgtctg tgagcctttc acacctgtgc tggcgctgga aaattatttg tgctcagctg 1560

acatttaaca cttcctcccc cgcttcctcc tagccctgtg ggcaggggtt ggaaacttag 1620

cactttatat ttatacagaa cattcaggat ttgtcaataa aatattgtta tatttaaaaa 1680

aaaaaaaaaa aaaaaaaaaa aa 1702

<210> 15
<211> 2473
<212> DNA
<213> Homo sapiens

<400> 15
aatcgcgaaa cccggcgagc ggcgcgctgg ctatcgagcg agcggggcgg aaccgggagt 60

tgcgccgccg ctcgggcgcc gggctccgtc gcggccgcag ccccgcgggt cgccctcccg 120

tgcctcgccc gcggacaccc tggccgtgga caccctggcc gtgggcaccc gcggggcgcg 180

gcgcgggcgc tgcgcggcgg cggcggcggc atgaaggtca cgtcgctcga cgggcgccag 240

ctgcgcaaga tgctccgcaa ggaggcggcg gcgcgctgcg tggtgctcga ctgccggccc 300

tatctggcct tcgctgcctc gaacgtgcgc ggctcgctca acgtcaacct caactcggtg 360

gtgctgcggc gggcccgggg cggcgcggtg tcggcgcgct acgtgctgcc cgacgaggcg 420

gcgcgcgcgc ggctcctgca ggagggcggc ggcggcgtcg cggccgtggt ggtgctggac 480

cagggcagcc gccactggca gaagctgcga gaggagagcg ccgcgcgtgt cgtcctcacc 540

tcgctactcg cttgcctacc cgccggcccg cgggtctact tcctcaaagg gggatatgag 600

actttctact cggaatatcc tgagtgttgc gtggatgtaa aacccatttc acaagagaag 660

attgagagtg agagagccct catcagccag tgtggaaaac cagtggtaaa tgtcagctac 720

aggccagctt atgaccaggg tggcccagtt gaaatccttc ccttcctcta ccttggaagt 780

gcctaccatg catccaagtg cgagttcctc gccaacttgc acatcacagc cctgctgaat 840

gtctcccgac ggacctccga ggcctgcatg acccacctac actacaaatg gatccctgtg 900

gaagacagcc acacggctga cattagctcc cactttcaag aagcaataga cttcattgac 960

tgtgtcaggg aaaagggagg caaggtcctg gtccactgtg aggctgggat ctcccgttca 1020

cccaccatct gcatggctta ccttatgaag accaagcagt tccgcctgaa ggaggccttc 1080

gattacatca agcagaggag gagcatggtc tcgcccaact ttggcttcat gggccagctc 1140

ctgcagtacg aatctgagat cctgccctcc acgcccaacc cccagcctcc ctcctgccaa 1200

ggggaggcag caggctcttc actgataggc catttgcaga cactgagccc tgacatgcag 1260

ggtgcctact gcacattccc tgcctcggtg ctggcaccgg tgcctaccca ctcaacagtc 1320

tcagagctca gcagaagccc tgtggcaacg gccacatcct gctaaaactg ggatggagga 1380

atcggcccag ccccaagagc aactgtgatt tttgttttta agactcatgg acatttcata 1440

cctgtgcaat actgaagacc tcattctgtc atgctgcccc agtgagatag tgagtggtca 1500

ccaggcttgc aaatgaactt cagacggacc tcagggtagg ttctcgggac tgaaggaagg 1560

ccaagccatt acgggagcac agcatgtgct gactactgta cttccagacc cctgccctct 1620

tgggactgcc cagtccttgc acctcagagt tcgccttttc atttcaagca taagccaata 1680

aatacctgca gcaacgtggg agaaagaagt tgctggacca ggagaaaagg cagttatgaa 1740

gccaattcat tttgaaggaa gcacaatttc caccttattt tttgaacttt ggcagtttca 1800

atgtctgtct ctgttgcttc ggggcataag ctgatcaccg tctagttggg aaagtcaccc 1860

tacagggttt gtagggacat gatcagcatc ctgatttgaa ccctgaaatg ttgtgtagac 1920

accctcttgg gtccaatgag gtagttggtt gaagtagcaa gatgttggct tttctggatt 1980

ttttttgcca tgggttcttc actgaccttg gactttggca tgattcttag tcatacttga 2040

acttgtctca ttccacctct tctcagagca actcttcctt tgggaaaaga gttcttcaga 2100

tcatagacca aaaaagtcat accttcgagg tggtagcagt agattccagg aggagaaggg 2160

tacttgctag gtatcctggg tcagtggcgg tgcaaactgg tttcctcagc tgcctgtcct 2220

tctgtgtgct tatgtctctt gtgacaattg ttttcctccc tgcccctgga ggttgtcttc 2280

aactgtggac ttctgggatt tgcagatttt gcaacgtggt actacttttt tttctttttg 2340

tctgttagtt atttctccag gggaaaaggc aataattttc taagacccgt gtgaatgtga 2400

agaaaagcag tatgttactg gttgttgttg ttgttcttgt tttttatatg taaaataaaa 2460

atagtgaaag gag 2473

<210> 16
<211> 2390
<212> DNA
<213> Homo sapiens

<400> 16
ccagcctcgg agggagggat tagaagccgc tagacttttt ttcctcccct ctcagtagca 60

cggagtccga attaattgga tttcattcac tggggaggaa caaaaactat ctgggcagct 120

tcattgagag agattcattg acactaagag ccagcgctgc agctggtgca gagagaacct 180

ccggctttga cttctgtctc gtctgcccca aggccgctag cctcggcttg ggaaggcgag 240

gcggaattaa accccgctcc gagagcgcac gttcgcgcgc ggtgcgtcgg ccattgcctg 300

ccccgagggg cgtctggtag gcaccccgcc ctctcccgca gctcgacccc catgatagat 360

acgctcagac ccgtgccctt cgcgtcggaa atggcgatca gcaagacggt ggcgtggctc 420

aacgagcagc tggagctggg caacgagcgg ctgctgctga tggactgccg gccgcaggag 480

ctatacgagt cgtcgcacat cgagtcggcc atcaacgtgg ccatcccggg catcatgctg 540

cggcgcctgc agaagggtaa cctgccggtg cgcgcgctct tcacgcgcgg cgaggaccgg 600

gaccgcttca cccggcgctg tggcaccgac acagtggtgc tctacgacga gagcagcagc 660

gactggaacg agaatacggg cggcgagtcg ttgctcgggc tgctgctcaa gaagctcaag 720

gacgagggct gccgggcgtt ctacctggaa ggtggcttca gtaagttcca agccgagttc 780

tccctgcatt gcgagaccaa tctagacggc tcgtgtagca gcagctcgcc gccgttgcca 840

gtgctggggc tcgggggcct gcggatcagc tctgactctt cctcggacat cgagtctgac 900

cttgaccgag accccaatag tgcaacagac tcggatggta gtccgctgtc caacagccag 960

ccttccttcc cagtggagat cttgcccttc ctctacttgg gctgtgccaa agactccacc 1020

aacttggacg tgttggagga attcggcatc aagtacatct tgaacgtcac ccccaatttg 1080

ccgaatctct ttgagaacgc aggagagttt aaatacaagc aaatccccat ctcggatcac 1140

tggagccaaa acctgtccca gtttttccct gaggccattt ctttcataga tgaagcccgg 1200

ggcaagaact gtggtgtctt ggtacattgc ttggctggca ttagccgctc agtcactgtg 1260

actgtggctt accttatgca gaagctcaat ctgtcgatga acgatgccta tgacattgtc 1320

aaaatgaaaa aatccaacat atcccctaac ttcaacttca tgggtcagct gctggacttc 1380

gagaggacgc tgggactcag cagcccatgt gacaacaggg ttccagcaca gcagctgtat 1440

tttaccaccc cttccaacca gaatgtatac caggtggact ctctgcaatc tacgtgaaag 1500

accccacacc cctccttgct ggaatgtgtc tggcccttca gcagtttctc ttggcagcat 1560

cagctgggct gctttctttg tgtgtggccc caggtgtcaa aatgacacca gctgtctgta 1620

ctagacaagg ttaccaagtg cggaattggt taatactaac agagagattt gctccattct 1680

ctttggaata acaggacatg ctgtatagat acaggcagta ggtttgctct gtacccatgt 1740

gtacagccta cccatgcagg gactgggatt cgaggacttc caggcgcata gggtagaacc 1800

aaatgatagg gtaggagcat gtgttcttta gggccttgta aggctgtttc cttttgcatc 1860

tggaactgac tatataattg tcttcaagtg aagactaatt caattttgca tatagaggag 1920

ccaaagagag atttcagctc tgtatttgtg gtatcagtgt tggaaaagag aaatctgata 1980

ctccatttgg attattgtaa atatttgatc ttgaatcact tgacagtgtt tgtttgaatt 2040

gtgtttgttt tttcctttga tgggcttaaa agaaattatc caaagggaga aagagcagta 2100

tgccacttct taaaacagaa caaaacaaaa aaagaaaatt gtgctctgtt gtaatccaaa 2160

ggggagattt gcagcatgct tgactttacc aattctgatg acatctttac ggacactatt 2220

atcactaaga ccttgttatg gcgaagtctt tagtcttttt catgtatttt cctcatgatt 2280

ttttctcttt atgtagtttg agtatgcctt acctttgtaa atatttttgc ttgtgttgtc 2340

gcaaagggga taatctggga aagacaccaa atcatgggct cactttaaaa 2390

<210> 17
<211> 1945
<212> DNA
<213> Homo sapiens

<400> 17
cgcggtgcgc gcggagggcc gggcgggcgg gcgggacgga ggccgggagg ccgggaggcc 60

ggggcggcgg gcgcgcagct cggcgggagg cgggcgcccg gagacgcggc tggggcccgc 120

gcggccgggg cgccgtccca gggcagggct gcccggcccc ggccccgggc cgcccgcgct 180

ccccatgaaa aaccagctcc gcggcccccc agcgcgggcg cacatgtcga cttcgggggc 240

ggcggcggct gggggcaccc gggcggggtc cgagcccggt gcggggtcgg ggtccggcgc 300

aggcaccggg gcgggcgcgg cgacgggggc aggggccatg ccctgcaaga gcgccgagtg 360

gctgcaggag gagctggagg cgcgcggcgg cgcgtccttg ctgctgctcg actgccggcc 420

gcacgagctc ttcgagtcgt cgcacatcga gacggccatc aacctggcca tcccgggcct 480

catgttgcgc cgcctgcgca agggcaacct gcccatccgc tccatcatcc ccaaccacgc 540

cgacaaggag cgcttcgcca cgcgctgcaa ggcggccacc gtgctgctct acgacgaggc 600

cacggccgag tggcagcccg agcccggcgc tcccgcctcc gtgctcggcc tgctcctaca 660

gaagctgcgc gacgacggct gccaggccta ctacctccaa ggtggtttca acaagtttca 720

aacagagtac tctgagcact gcgagaccaa cgtggacagc tcttcctcgc cgagcagctc 780

gccacccacc tcagtgctgg gcctgggggg cctgcgcatc agctctgact gctccgacgg 840

cgagtcggac cgagagctgc ccagcagtgc caccgagtca gacggcagcc ctgtgccatc 900

cagccaacca gccttccctg tccagatcct gccctacctc tacctcggct gcgccaagga 960

ctccaccaac ctggacgtgc tcggcaagta tggcatcaag tatatcctca atgtcacacc 1020

caacctaccc aacgccttcg agcacggcgg cgagttcacc tacaagcaga tccccatctc 1080

tgaccactgg agccagaacc tctcccagtt cttccctgag gccatcagct tcattgacga 1140

agcccgctcc aagaagtgtg gtgtcctggt gcactgcctg gcaggcatca gccgctcagt 1200

gacggtcact gtggcctatc tgatgcagaa gatgaacctg tcactcaacg acgcctacga 1260

ctttgtcaag aggaaaaagt ccaacatctc gcccaacttc aacttcatgg ggcagctgct 1320

ggactttgag cggacgctgg ggctaagcag cccgtgcgac aaccacgcgt cgagtgagca 1380

gctctacttt tccacgccca ccaaccacaa cctgttccca ctcaatacgc tggagtccac 1440

gtgaggcctg gtgcacgggg ggcatggcac caggcccctg ctcggctctc cacagggcta 1500

ggtgggagag cccaagcccg ccacctctgg cctgaggaac ccccagatgt cacctgtgcc 1560

cagaggccca ggctgatcgg tgtcggagcg cccctcacca tccttggggg cagggcccgc 1620

aggcaaggtc tcccactgca gggcttgctg gagaggcctc ggctcttgga cacgtggctt 1680

tgggcgtcca ccagggcctc atcctgtcca ggacgctcct ttctgctgac agcccagcca 1740

gtttggctgt tttttaaaga cacatccacg gacctgagtt tacttttttac ttttggcagg 1800

taaatccaag ctccctggag cacaaagagt gtttgagctc ttcttgattt ttctttttttt 1860

ttttttttttt taacaaaaag tgttattttc aggctacatg caacagtgga ttgtataacc 1920

cagtatttca tccctttcct gatcc 1945

<210> 18
<211> 2377
<212> DNA
<213> Homo sapiens

<400> 18
ggggagccga ggcgagcgcg agcgaggtcc agcaccatgt gctaggtcac tcccagcgcg 60

aggccacacc tgggccgtcg gagcagcccc tcctcacttc aggggtcacc ctccccagca 120

cccattgccc caccatggct ggggaccggc tcccgaggaa ggtgatggat gccaagaagc 180

tggccagcct gctgcggggc gggcctgggg ggccgctggt catcgacagc cgctccttcg 240

tggagtacaa cagctggcat gtgctcagct ccgtcaacat ctgctgctcc aagctggtga 300

agcggcggct gcagcagggc aaggtgacca ttgcggagct catccagccg gctgcacgca 360

gccaggtgga ggctacggag ccacaggacg tggtggtcta tgaccagagc acgcgggacg 420

ccagcgtgct ggccgcagac agcttcctct ccatcctgct gagcaagctg gacggctgct 480

tcgacagcgt ggccatcctc actgggggct tcgccacctt ctcctcctgc ttccccggcc 540

tctgcgaggg caagcctgct gccctgctac ccatgagcct ctcccagccc tgcctgcctg 600

tgcccagcgt gggcctgacc cgcatcctgc ctcacctcta cctgggctcg cagaaggacg 660

tcctaaacaa ggatctgatg acgcaaaatg gaataagcta cgtcctcaac gccagcaact 720

cctgccccaa gcctgacttc atctgcgaga gccgcttcat gcgggtcccc atcaacgaca 780

actactgtga aaaactgctg ccctggctgg acaagtccat cgagttcatc gataaagcca 840

agctctccag ctgccaagtc atcgtccact gtctggctgg catctcccgc tctgccacca 900

tcgccatcgc ctacatcatg aagaccatgg gcatgtcctc cgacgacgcc tacaggttcg 960

tgaaggacag gcgcccgtcc atctcgccca acttcaactt cctgggccag ctgctggagt 1020

acgagcgcac gctgaagctg ctggccgccc tgcagggcga cccgggcacc ccctcaggga 1080

cgccggagcc tccgcccagt cctgccgccg gggccccgct gccacggctg ccaccaccta 1140

cctcagagag cgctgccaca gggaatgcgg ctgccaggga gggcggcctg agcgcgggcg 1200

gggagccccc cgcgcccccc acgccccggg cgaccagcgc actgcagcag ggcctgcgcg 1260

gcctgcacct ctcctcggac cgcctgcagg acactaaccg cctcaagcgc tccttctccc 1320

tggacatcaa gtctgcctac gcccctagca ggcggcccga cggccccggg ccccccgacc 1380

ccggcgaggc cccgaagctc tgcaagctgg acagcccgtc gggggccgcg ctgggcctgt 1440

cctcgcccag cccggacagc ccggacgccg cgcctgaggc gcgcccacgg ccccgccggc 1500

ggccccggcc ccccgccggc tcccccgcgc gctcccccgc gcacagcctc ggcctgaact 1560

tcggcgatgc ggcccggcag actccgcggc acggcctctc ggccctgtcg gcgcccgggc 1620

tgcccggccc tggccagccg gccggccccg gggcctgggc accgccgctt gactccccag 1680

gcacgccgtc gcccgacggg ccctggtgct tcagccccga gggcgcacag ggggcgggcg 1740

gggtgctgtt tgcgcccttc ggccgggcgg gcgccccggg accaggcggc ggcagcgacc 1800

tgcggcggcg ggaggcagcg agggctgagc cccgggacgc gcggaccggc tggcccgagg 1860

agccggcccc ggagacgcag ttcaagcgcc gcagctgcca gatggagttc gaggagggca 1920

tggtggaggg gcgcgcgcgc ggcgaggagc tggccgccct gggcaagcag gcgagcttct 1980

cgggcagcgt ggaggtcatc gaggtgtcct gacccctccg ctgccctcgg ccccgccgcc 2040

cgcagccagg cccgttataa atgtatatta tatataatgc aaagaaaggt aaatggtttt 2100

actgggattt ttatcgagaa gtaaatattt cgatttttta tttatttaag ctgttcattc 2160

tggcaatgat ttggcaacag tgcgggtggt cctcgagctc tatttttact gtctggtatt 2220

taaactgaaa catacgtttc taagcaatac gaggccacct tcagtcgcaa gctgggtgcc 2280

aggcctgggg ccctcccagt tcccccgccc caggaaacac tgctgacctt tgcaaaggct 2340

gccgagcttt cgtgcacttt ttacataaca aaaaggg 2377

<210> 19
<211> 2303
<212> DNA
<213> Homo sapiens

<400> 19
cgcttcccgc cgcccgagct tcggaaactt cccggccgcg acgcagggaa ccggcgcgga 60

gaaccgagca gagcggagcg cccgtggtcc agcgtgtagg gagccgatcg cccatggagg 120

gtctgggccg ctcgtgcctg tggctgcgtc gggagctgtc gcccccgcgg ccgcggctcc 180

tgctcctgga ctgccgcagc cgcgagctgt acgagtcggc gcgcatcggt ggggcgctga 240

gcgtggccct gccggcgctc ctgctgcgcc gcctgcggag gggcagcctg tcggtgcgcg 300

cgctcctgcc tgggccgccg ctgcagccgc ccccgcctgc ccccgtgctc ctgtacgacc 360

agggcggggg ccggcgccgg cgcggggagg ccgaggccga ggccgaggag tgggaggccg 420

agtcggtgct gggcaccctg ctgcagaagc tgcgagagga aggctacctg gcctactacc 480

tccagggagg cttcagcaga ttccaggccg agtgccctca cctgtgtgag accagccttg 540

ctggccgtgc cggctccagc atggcgccgg tgcccggtcc agtgcccgtg gtggggttgg 600

gcagcctgtg cctgggctcc gactgctctg atgcggaatc cgaggctgac cgcgactcca 660

tgagctgtgg cctggattcg gagggtgcca cacccccacc agtggggctg cgggcatcct 720

tccctgtcca gatcctgccc aacctctatc tgggcagtgc ccgggattcc gccaatttgg 780

agagcctggc caaactgggc atccgctaca tcctcaatgt cacccccaac ctcccaaact 840

tcttcgagaa gaatggtgac tttcactaca agcagatccc catctccgac cactggagcc 900

agaacctgtc gcggttcttt ccggaggcca ttgagttcat tgatgaggcc ttgtcccaga 960

actgcggggt gctcgtccac tgcttggcgg gggtcagccg ttctgtcacc gtcactgtgg 1020

cctacctcat gcagaagctc cacctctctc tcaacgatgc ctatgacctg gtcaagagga 1080

agaagtctaa catctccccc aacttcaact tcatggggca gttgctggac tttgagcgca 1140

gcttgcggct ggaggagcgc cactcgcagg agcagggcag tgggggggcag gcatctgcgg 1200

cctccaaccc gccctccttc ttcaccaccc ccaccagtga tggcgccttc gagctggccc 1260

ccacctaggg ccccgtggcc ggcaggccgg cccctgcccc acccccaccc acgggtgtcc 1320

ctgcccactc gtgtggcaag ggaggggagg gcaggagggc tcggcctgag cagggtgctg 1380

gggggagagc gcaatacctc acgcgggctg ccgtcctaat caacgtgcct atggcgggac 1440

cacgctcgga gcctgcctct tctgcgactg ttacttttтc tttgcgggat gggggtgggg 1500

gttccctctc caggtggttg tccaagccca ggtcccggcc ctgggtgctc agccagctcg 1560

gctaggccct gcgcctccct gcgcttcccc cttcaggaag ggtgtgtgcc acctcgttgc 1620

actggatccc agtggctgct tgggggagag gcgtttgcca tcactggtgt tgtcacctcc 1680

ctgtttctcc accaagggct tgggcctctc ggggctgggg cctcccaggg gatggggacc 1740

cagaggtgca gtggccgccc acatccatgg cctaggagct actgggcagg ttcccggcca 1800

cacatctggt gggctgtttt gtttttttтt ttcctcttcc cccagatgtc ttgacgggat 1860

cactggggct ctttgtgagt gagggtggcc aaactaccgc cggaggagat ggggtctcag 1920

agcgagagct gcggaggggg aggggaagaa gaaggcctca cttttgctgc tgcggggccc 1980

acacagccgc tgctactttg gggggtgggg aaggggccaa gctgcagaca cacacagtca 2040

ttcatttctg tccacacccc tgtgggtggc gggtgtgcgt gtgtgtgctt gtgtgtgcgc 2100

acgtgtcggc gctcacacac acatgctagc ccactgatgc acccagccca gggctggcag 2160

tctttgcagc gtggggccgt ctcaccctgg agcctggaga ggatctatgc ttgtttgttt 2220

ttgtaatcca tatcatagtt gctttcttta attgttcctt ctgaataaac agtttattta 2280

agataaaaaa aaaaaaaaaa aaa 2303

<210> 20
<211> 2505
<212> DNA
<213> Homo sapiens

<400> 20
gctgagcgcc ggaggagcgt aggcagggca gcgctggcgc cagcggcgac aggagccgcg 60

cgaccggcaa aaatacacgg gaggccgtcg ccgaaaagag tccgcggtcc tctctcgtaa 120

acacactctc ctccaccggc gcctccccct ccgctctgcg cgccgcccgg ctgggcgccc 180

gaggccgctc cgactgctat gtgaccgcga ggctgcggga ggaaggggac agggaagaag 240

aggctctccc gcgggagccc ttgaggacca agtttgcggc cacttctgca ggcgtccctt 300

cttagctctc gcctgccccc ttctgcagcc taggcggccc aggttctctt ctcttcctcg 360

cgcgcccagc cgcctcggtt cccggcgacc atggtgacga tggaggagct gcgggagatg 420

gactgcagtg tgctcaaaag gctgatgaac cgggacgaga atggcggcgg cgcgggcggc 480

agcggcagcc acggcaccct ggggctgccg agcggcggca agtgcctgct gctggactgc 540

agaccgttcc tggcgcacag cgcgggctac atcctaggtt cggtcaacgt gcgctgtaac 600

accatcgtgc ggcggcgggc taagggctcc gtgagcctgg agcagatcct gcccgccgag 660

gaggaggtac gcgcccgctt gcgctccggc ctctactcgg cggtcatcgt ctacgacgag 720

cgcagcccgc gcgccgagag cctccgcgag gacagcaccg tgtcgctggt ggtgcaggcg 780

ctgcgccgca acgccgagcg caccgacatc tgcctgctca aaggcggcta tgagaggttt 840

tcctccgagt acccagaatt ctgttctaaa accaaggccc tggcagccat cccacccccg 900

gttccccccа gcgccacaga gcccttggac ctgggctgca gctcctgtgg gaccccacta 960

cacgaccagg ggggtcctgt ggagatcctt cccttcctct acctcggcag tgcctaccat 1020

gctgcccgga gagacatgct ggacgccctg ggcatcacgg ctctgttgaa tgtctcctcg 1080

gactgcccaa accactttga aggacactat cagtacaagt gcatcccagt ggaagataac 1140

cacaaggccg acatcagctc ctggttcatg gaagccatag agtacatcga tgccgtgaag 1200

gactgccgtg ggcgcgtgct ggtgcactgc caggcgggca tctcgcggtc ggccaccatc 1260

tgcctggcct acctgatgat gaagaaacgg gtgaggctgg aggaggcctt cgagttcgtt 1320

aagcagcgcc gcagcatcat ctcgcccaac ttcagcttca tggggcagct gctgcagttc 1380

gagtcccagg tgctggccac gtcctgtgct gcggaggctg ctagcccctc gggacccctg 1440

cgggagcggg gcaagacccc cgccaccccc acctcgcagt tcgtcttcag ctttccggtc 1500

tccgtgggcg tgcactcggc ccccagcagc ctgccctacc tgcacagccc catcaccacc 1560

tctcccagct gttagagccg ccctgggggc cccagaacca gagctggctc ccagcaaggg 1620

taggacgggc cgcatgcggc agaaagttgg gactgagcag ctgggagcag gcgaccgagc 1680

tccttcccca tcatttctcc ttggccaacg acgaggccag ccagaatggc aataaggact 1740

ccgaatacat aataaaagca aacagaacac tccaacttag agcaataacc ggtgccgcag 1800

cagccaggga agaccttggt ttggtttatg tgtcagtttc acttttccga tagaaatttc 1860

ttacctcatt tttttaagca gtaaggcttg aagtgatgaa acccacagat cctagcaaat 1920

gtgcccaacc agctttacta aaggggggagg aagggagggc aaagggatga gaagacaagt 1980

ttcccagaag tgcctggttc tgggtacttg tccctttgtt gtcgttgttg tagttaaagg 2040

aatttcattt ttaaaagaaa tcttcgaagg tgtggttttc atttctcagt caccaacaga 2100

tgaataatta tgcttaataa taaagtattt attaagactt tcttcagagt atgaaagtac 2160

aaaaagtcta gttacagtgg atttagaata tatttatgtt gatgtcaaac agctgagcac 2220

cgtagcatgc agatgtcaag gcagttagga agtaaatggt gtcttgtaga tatgtgcaag 2280

gtagcatgat gagcaacttg agtttgttgc cactgagaag caggcgggtt gggtgggagg 2340

aggaagaaag ggaagaatta ggtttgaatt gctttttaaa aaaaaaagaa aagaaaaaga 2400

cagcatctca ctatgttgcc aaggctcatc ttgagaagca ggcgggttgg gtgggaggag 2460

gaagaaaggg aagaattagg tttgaattgc ttttttaaaa aaaaa 2505

<210> 21
<211> 3488
<212> DNA
<213> Homo sapiens

<400> 21
agcagctccg gcggccgaga cgggggcggc ggccgcgcgg gtctggcggg accggtttgg 60

aagactttgc cggcctgcag attggcctta agagaaggac ggagccacat actgctgacg 120

gcccagaact ggcagagaga aggttgccat ggctgctgtt gacagtttct acctcttgta 180

cagggaaatc gccaggtctt gcaattgcta tatggaagct ctagctttgg ttggagcctg 240

gtatacggcc agaaaaagca tcactgtcat ctgtgacttt tacagcctga tcaggctgca 300

ttttatcccc cgcctgggga gcagagcaga cttgatcaag cagtatggaa gatgggccgt 360

tgtcagcggt gcaacagatg ggattggaaa agcctacgct gaagagttag caagccgagg 420

tctcaatata atcctgatta gtcggaacga ggagaagttg caggttgttg ctaaagacat 480

agccgacacg tacaaagtgg aaactgatat tatagttgcg gacttcagca gcggtcgtga 540

gatctacctt ccaattcgag aagccctgaa ggacaaagac gttggcatct tggtaaataa 600

cgtgggtgtg ttttatccct acccgcagta tttcactcag ctgtccgagg acaagctctg 660

ggacatcata aatgtgaaca ttgccgccgc tagtttgatg gtccatgttg tgttaccggg 720

aatggtggag agaaagaaag gtgccatcgt cacgatctct tctggctcct gctgcaaacc 780

cactcctcag ctggctgcat tttctgcttc taaggcttat ttagaccact tcagcagagc 840

cttgcaatat gaatatgcct ctaaaggaat ctttgtacag agtctaatcc ctttctatgt 900

agccaccagc atgacagcac ccagcaactt tctgcacagg tgctcgtggt tggtgccttc 960

gccaaaagtc tatgcacatc atgctgtttc tactcttggg atttccaaaa ggaccacagg 1020

atattggtcc cattctattc agtttctttt tgcacagtat atgcctgaat ggctctgggt 1080

gtggggagca aatattctca accgttcact acgtaaggaa gccttatgct gcacagcctg 1140

agtctggatg gccacttgag aagttttgcc aactcctggg aacctcgata ttctgacatt 1200

tggaaaaaca catttaattt atctcctgtg tttcattgct gattattcag catactgttg 1260

attcgtcatt tgcaaaacac acataatacc gtcagagtgc tgtgaaaaac cttaagggtg 1320

tgtggatggc acaggatcaa taatgcctga ggctgattga cgacatctac atttcagtgc 1380

tttttcccta agctgtttga aagttacgct tttctgttgt tctagagcca cagcagtcta 1440

atattgaaat ataatatgat ttgtcaggtc ttataatttc agatgttgtt ttttaaggga 1500

aattgaccat ttcactagag gagttgtgct ggtttttaaa tgtgcatcaa gaaagactac 1560

tgaaaagtat tattttgtaa ctaagattgc tggtactatt aggaaaaatc tgtgtgtatc 1620

gtatagctct agctgtttga ctatctgtaa tgaaaatgct gcacttcaac tggtatttca 1680

ttagagaacc gtgtgtgtgc gtgtgtgtgg tgcctttgag caactttatt tatggttacc 1740

atatttttaa aaagattttt tgtcaggatg acttaacatg gactcttata gggtattaaa 1800

acaatctaga ttattccttt tcatcctaaa taagcctacc aaatttcatg ctgttggttt 1860

gccatgaatg atattacttc ctacattata tttgtgtttt ttcaaatctg ctatggaatg 1920

aacttattcc tagatttgga tatgtaagag aaacctgcag tcatcttttg atttataagg 1980

caattcttgt ggataaatag tgatttctca gcctctgacc cattttataa ctgaaattta 2040

gcccttttaga gcttgttata tctggttttc ctacgttttt ctatgtaata ttattccatt 2100

ccagtagcat tattgataga aatagtaagt atttatggaa tagtaaaata tggacaaatt 2160

acgtgtgtga catatctgtc aaaataagtt agaagcttat tcttggtttg tgtaatgaat 2220

ttatgtattg tagtgaatac ctttactggt gtgaagataa ttatgcacaa accctcacaa 2280

tacgcgttaa cattgaaacc tgtgaaatgt ccttaggttg ggtcatataa agccaaccat 2340

ttttgaggac catgtaccta gtgctttgaa aactgtaagt cactatatga atatgacaat 2400

atgtgcacat ttaaaattca gagctcggca ttgtgatact gatgcagaag ctagtagatt 2460

ggttaaaagt ctggacttct gtggcatttt tttcgtgacg tgataatcta tcataagcag 2520

acctaagcac agttttatga acacaatttt gcccatgaca ttgcctacag gatttccaga 2580

tgtgacttgc actcagaaga tcagtggtca acttcagaag ctcttccacg cttagatcat 2640

gtcttcagaa cttagatgtg aaaatctaca cactgggaga tgctgtgagc cccaaggttt 2700

tgatggagtt tgcttggaat cctcttgact tcatgccaca ttgacgtgaa ctttgatgta 2760

taataagcag cagcaacttc atgtgaaaat atggtcaggt agttatatgt aaggttacgt 2820

ggtccagtaa tgtcttagat tgataaatta ggtatggaat ccatcagtgt tacgtgatga 2880

gaataggtga acacaccttg tcagtgatga tgtaaacttc tctccttggc agggcatggg 2940

caaacatgct gattggtgca aatgtggtgc cgagctgtcc atagctgcag tgaaaggtga 3000

agagcaagac cttctctagg ttttctagct ttcattaaat gtatttttt ccccagagct 3060

aatttgaaag ttgattggac cactgtggat ggggtctcat taagaatgtg ggaaataggg 3120

gccgagtgcg gtggctcaca cctgtaatcc cagcagtttg gaaggccagg gcaggtggat 3180

cgcttgatcc caggaggtcg agaccagcct ggggaacaca tcctgtctct acaaaaaata 3240

caaaaattag ccaggcaggg tggtgcatgc ctgtagtccc agctacttgg gaggctgagg 3300

caggagaatt ttttgagccc aggatgcaga ggttgaagtg agccaagatc gtgccactgc 3360

actccagcct tgagacagag cgagaccctg tctcaaaaaa aaaaaaagaa cgtgggaaat 3420

atgaaccttt gaaagttaat ctgtgaattg aaagtttaac aataaaagta gttgtttgtt 3480

tcctttgg 3488

<210> 22
<211> 3058
<212> DNA
<213> Homo sapiens

<400> 22
ccgggccgca gcatggccga gccgctactc aggaaaacct tctcccgcct gcggggccgg 60

gagaaacttc cccggaaaaa gtcggacgcc aaggagcgcg ggcctggggt acctggcact 120

ggggagcccg ccggcgagat ctggtacaac cccatccctg aggaagaccc cagacctcca 180

gcacctgagc ccccggggcc acagcctggc tcagctgagt cagagggcct ggccccccaa 240

ggtgcagccc ccgccagccc cccaaccaaa gcctcccgca ccaagtcccc gggccccgcc 300

aggcgcctct ccataaagat gaagaagctg ccggaactgc ggcgccgcct gagcctgcga 360

ggcccccggg ctggcaggga gcgcgagagg gctgcccctg cgggctccgt catcagccgc 420

taccacctgg acagcagcgt ggggggcccc gggccggcag cagggcctgg gggcacccgg 480

agcccgaggg ccggttacct cagcgacggg gactcaccgg agcgcccagc tgggccccca 540

tcacccacct ccttccggcc ctacgaggtg ggtcccgcag cccgggcacc cccggccgca 600

ctctggggcc gcctcagcct gcacctgtac ggtctcgggg ggctgcggcc agcgccgggg 660

gccacccccа gggacctctg ctgcctactg caagtggatg gggaggccag ggcccgaaca 720

gggccactgc gaggggggcc ggacttcctg cggctggacc acaccttcca cctggagctg 780

gaggccgcca ggctcctgcg cgccctggtg cttgcgtggg accctggcgt gagaaggcac 840

cggccctgtg cccagggcac cgtgctgctg cccacggtct tccgagggtg ccaggcccaa 900

cagctggccg tgcgcctgga gcctcagggg ctgctgtatg ccaagctgac cctgtcggag 960

cagcaggaag cccctgccac agctgagccc cgcgtctttg ggctgcccct gccactgctg 1020

gtggagcggg agcggccccc cggccaggtg cccctcatca tccagaagtg cgttgggcag 1080

atcgagcgcc gagggctgcg ggtagtggga ctgtaccgtc tttgtggctc agcggcagtg 1140

aagaaagagc ttcgggatgc ctttgagcgg gacagtgcag cggtctgcct atctgaggac 1200

ctgtaccccg atatcaatgt catcactggc atcctcaagg attatcttcg agagttgccc 1260

accccactca tcacccagcc cctgtataag gtggtactgg aggccatggc ccgggacccc 1320

ccaaacagag ttcccccccac cactgagggc acccgagggc tcctcagctg cctgccagat 1380

gtggaaaggg ccacgctgac gcttctcctg gaccacctgc gcctcgtctc ctccttccat 1440

gcctacaacc gcatgacccc acagaacttg gccgtgtgct tcgggcctgt gctgctgccg 1500

gcacgccagg cgcccacaag gcctcgtgcc cgcagctccg gcccaggcct tgccagtgca 1560

gtggacttca agcaccacat cgaggtgctg cactacctgc tgcagtcttg gccagatccc 1620

cgcctgcccc gacaatctcc agatgtcgcg ccttacttgc gacccaaacg acagccacct 1680

ctgcacctgc cgctggcaga ccccgaagtg gtgactcggc cccgcggtcg aggaggcccc 1740

gaaagccccc cgagcaaccg ctacgccggc gactggagcg tttgcgggcg ggacttcctg 1800

ccctgtgggc gggatttcct gtccgggcca gactacgacc acgtgacggg cagtgacagc 1860

gaggacgagg acgaggaggt cggcgagccg agggtcaccg gtgacttcga agacgacttc 1920

gatgcgccct tcaacccgca cctgaatctc aaagacttcg acgccctcat cctggatctg 1980

gagagagagc tctccaagca aatcaacgtg tgcctctgag ccagatgacg gggtgggacc 2040

ccggttagta aggaccgggc gcccagtggc taaggcggtg ccctggtgac caaggagagc 2100

cagacctgtt gctcaggccg agctcctggt tgccagcgag ttaccacggg accagtcgcg 2160

tgtatggctg agactcattc ccagtttcca gggcccggta tttggacact agttgccaag 2220

tctggggcct ggggatttta gggaccagcg gttgtgacca tctttcctga gcaccaaggg 2280

cttccccttt tgttgccaaa aaggtagttc tcgcgcttgc taggctggcc tctcttgcct 2340

ccccttggcc ggggcaacac cagttactgt gagcatcacc ctggtgtggt gagtcacctc 2400

tagtcggccc tcttgctgct gccaaccaaa tcagtattag ctttgagcac tgcactgttt 2460

ctccctccct tggacgacac aaagactagc atgaggcact gtttgtgggg ggcagcccct 2520

atcctgggtt ccagcatgga cacaggggta gcctggggct tatagagaaa cagctggttt 2580

cccctaccct tttccgggga agaccccacg attggcctct agtcagcaaa tggagataac 2640

agagtctggc ctttccaatc cccatctcct tgcccccccc ttgcccccccc cccgaaaaaa 2700

attgagcact taaacccctc ccttttggag ggggccccct gaagcgtcag gctgggggca 2760

gtctggtacg gaacatattt attgcctcca tgcatgtgtg tgtgtgtctg tgaggactgg 2820

tgtgcgtgga cacgtctgaa gcaggcgtgt ggggctcttt cagggaccac agaggaggga 2880

gcagtttgca gtgcccagcc accctgaaat ccccaataat ggtgcctcag tgggccccag 2940

agttccagtg ggagagtacg gttccctcct gtctccctct tcttttccgc acctccatct 3000

ttgtggataa taaataaata tgcacaggtt ctgagactga aaaaaaaaaa aaaaaaaa 3058

<210> 23
<211> 2949
<212> DNA
<213> Homo sapiens

<400> 23
gcgtaccttt ctccaggttt tcagcctgtg atttgataac cgccgccggg tggcgtggag 60

cgtcccgaga cttcttcctt cattgcagcc cctcttcttt tagttctaga ctgaagttcg 120

aggaacgcac cacttggctg aaattaggat ccagatttcc caaacttcct tcggaggaaa 180

aagccctaac gatggaggac agtgaattcc tagcttatgt ggaactacta gatgaagtgg 240

aacaaggctc agtgagagca aaagcatctt ctgttagtct acatgcagaa agaacctgga 300

tggagaaaat gaaagttgaa gacctaaatg tatgtgagcc tgcttctcct gcccctgaag 360

caccagctac ctctctgctg aatgacctca agtacagccc atcagaggaa gaggaggtga 420

catacacagt cattaatcaa ttccagcaga agtttggtgc tgcgatactc catatcaaga 480

agcagaatgt cctgagtgtg gcagcagaag gagcgaatgt atgtcgccat ggcaaactgt 540

gctggctgca ggtggccaca aattgccgag tttacttatt tgacattttc cttctgggaa 600

gtcgagcttt ccacaatgga cttcagatga tactagaaga caagagaatt ttgaaggtta 660

tccatgattg tcgttggctt tctgattgcc tctctcatca gtatggaatt ttgctgaata 720

atgtctttga cacacaggta gcagatgtac ttcagttttc catggaaacg ggtggctatc 780

ttccaaactg catcactact ttgcaggaga gtttaatcaa acaccttcaa gtagccccta 840

aatatctctc ctttctagaa aagagacaaa aactaattca ggaaaatcca gaagtatggt 900

tcatccgacc tgtttcaccc tctttactga aaattttggc cctggaagct acctacctgt 960

taccccttcg cttggcactc ctagatgaga tgatgtctga cctaaccacc ctggtggatg 1020

gttacctaaa cacgtatcgc gaagggtctg cagaccggct tggaggcact gagcctacat 1080

gtatggagct gccagaggaa ctgcttcaac tcaaggactt ccagaagcag cgcagggaga 1140

aagctgcaag agaatatagg gtgaatgcac agggactcct gataaggaca gtgctacagc 1200

caaagaaatt agtgacagag acagcaggga aagaggagaa agtcaaaggc ttcttatttg 1260

gtaaaaattt taggatagat aaagctccaa gttttacatc tcaagacttt cacggggatg 1320

tgaatttact gaaagaagaa tctttgaata aacaagctac aaatcctcaa catctacctc 1380

ccacggagga aggggaaact agtgaggatt ccagtaacaa actcatttgc acaaagtcaa 1440

aggggtcaga ggaccagaga ataactcaga aagaacactt tatgacaccc aaacatgagt 1500

ttcaggcaag tttatctttg aaagaggaga cagaacagtt attgatggtg gaaaacaagg 1560

aagatttaaa atgcacaaaa caggctgttt caatgtcttc ctttcctcag gaaaccagag 1620

tgtctccaag tgacactttt tatcctatca gaaagactgt ggtttccaca ctccctccct 1680

gtccagcctt ggagaagatc gattcctgga taagtccttt tctaaatctg ccctagagat 1740

gggcagtttg ttcttaaggc catgcagatg gcttatttcc tttgccatca gggctttcca 1800

cagtgcccag gtttctcatg ttgtaaatgt agtaatgctt cagtcacagg ggaaaattat 1860

atcctcttgc ttactcctgt gttcctggta tgcggagaat gagaatgaat aagttaaata 1920

atggaagaag tataatttct gattatgtca ctgtgtagaa atgttctcag tgaccagagt 1980

gcattatttt tcataatttg ggtttagagg atttgaagaa aggaagaatc ttgggcttag 2040

tatcaggaag actccatcat tttcaaattt tgttttgctt cttgactttt ggattccttt 2100

gaagagacct ggtaaaacta ttaacaattc atttaaaaaa ttggtacctg ataactttac 2160

cagtactttt ttccttttta tttatttgtt ttatttattt ttttttaccg ctccttgtgg 2220

agcagggcta caccataggc agtgtgccca gagtaaccac ttttttcctt tttaaaatat 2280

aatattaact ttatgtttga atgttgaatg ttttgtctgt ctcttaggca aataatgtta 2340

taggaatcaa taatttaatt tttgttttat ttgttttttg atggagtctc actctgtcac 2400

ccaggctgga gtgtagtggt gtaatctctg ctcactgcaa cctccgcctc ccgggttcaa 2460

gcaattctcc tgcctcagcc tcctgagtag ctgggattac aggtgcgtgc caccacgccc 2520

ggctaatttt tgtattttta gtagagatgg ggtttcacca tgttggccag gctggtctcg 2580

aactcctgac tgaccttgtg gtccacctgc cttggccttc caaagtgctg ggattacagg 2640

tgtgaggcac ggtgcccagc caatatcttt attttaattt gtttttattt cctttatttt 2700

tagctggttt tgtccatttt cctaacaaag cagggaccct gggtttcttt ttagtctgtc 2760

tgttatataa acttgaagcc tgactccatt ctatttgcct ggagttagta tactttctta 2820

gggtgaaagg aaggcagctt gtattgagcc ttttaaagta ttgaatgctt gcaaattgct 2880

aacattcttt tgtgtaaaat aaccaataaa cctgttttgt catactctac ttaaaaaaaa 2940

aaaaaaaaa 2949

<210> 24
<211> 3230
<212> DNA
<213> Homo sapiens

<400> 24
actttccggg atggcagcaa ggtgacttcg gctgaggatg accctgactg aaaggctgcg 60

tgagaagata tctcgggcct tctacaacca tgggctcctc tgtgcatcct atcccatccc 120

catcatcctc ttcacagggt tctgcatctt agcctgctgc tacccactgc tgaaactccc 180

cttgccagga acaggacctg tggaattcac cacccctgtg aaggattact cgcccccacc 240

tgtggactct gaccgcaaac aaggagagcc tactgagcag cctgagtggc gagattttcc 300

cctaccttgt ggtggttatt gggttagaga atgtgttggt gctcaccaag tctgtggtct 360

caaccccggt agacctggag gtgaagctgc ggatcgccca aggcctaagc agcgagagct 420

ggtccatcat gaagaacatg gccacggagc tgggcatcat cctcatcggc tacttcaccc 480

tagtgcccgc catccaggag ttctgtctct ttgctgtcgt ggggctggtg tctgacttct 540

tccttcagat gctgtttttc accactgtcc tgtccattga cattcgccgg atggagctag 600

cagacctgaa caagcgactg ccccctgagg cctgcctgcc ctcagccaag ccagtggggc 660

agccaacgcg ctacgagcgg cagctggctg tgaggccgtc cacaccccac accatcacgt 720

tgcagccgtc ttccttccga aacctgcggc tccccaagag gctgcgtgtt gtctacttcc 780

tggcccgcac ccgcctggca cagcgcctca tcatggctgg caccgttgtc tggattggca 840

tcctggtata cacagaccca gcagggctgc gcaactacct cgctgcccag gtgacggaac 900

agagcccatt gggtgaggga gccctggctc ccatgcccgt gcctagtggc atgctgcccc 960

ccagccaccc ggaccctgcc ttctccatct tcccacctga tgcccctaag ctacctgaga 1020

accagacgtc gccaggcgag tcacctgagc gtggaggtcc agcagaggtt gtccatgaca 1080

gcccagtccc agaggtaacc agggggcctg aggatgagga actttggagg aaattgtcct 1140

tccgccactg gccgacgctc ttcagctatt acaacatcac actggccaag aggtacatca 1200

gcctgctgcc cgtcatccca gtcacgctcc gcctgaaccc gagggaggct ctggagggcc 1260

ggcaccctca ggacggccgc agtgcctggc ccccaccggg gcccatacct gctgggcact 1320

gggaagcagg acccaagggc ccaggtgggg tgcaggccca tggagacgtc acgctgtaca 1380

aggtggcggc gctgggcctg gccaccggca tcgtcttggt gctgctgctg ctctgcctct 1440

accgcgtgct atgcccgcgc aactacgggc agctgggtgg tgggcccggg cggcggaggc 1500

gcggggagca gccctgcgac gactacggct atgcgccacc cgagacggag atcgtgccgc 1560

ttgtgctgcg cggccacctc atggacatcg agtgcctggc cagcgacggc atgctgctgg 1620

tgagctgctg cctggcaggc cacatctgcg tgtgggacgc gcagaccggg gattgcctaa 1680

cgcgcattcc gcgcccaggg cagcgccggg acagtggcgt gggcagcggg cttgaggctc 1740

aggagagctg ggaacgactt tcagatggtg ggaaggctgg tccagaggag cctggggaca 1800

gccctcccct gagacaccgc ccccggggcc ctccgccgcc ttccctcttc ggggaccagc 1860

ctgacctcac ctgcttaatt gacaccaact tttcagcgca gcctcggtcc tcacagccca 1920

ctcagcccga gccccggcac cgggcggtct gtggccgctc tcgggactcc ccaggctatg 1980

acttcagctg cctggtgcag cgggtgtacc aggaggaggg gctggcggcc gtctgcacac 2040

cagccctgcg cccaccctcg cctgggccgg cgctgtccca ggcccctgag gacgagggtg 2100

gctcccccga gaaaggctcc ccttccctcg cctgggcccc cagtgccgag ggttccatct 2160

ggagcttgga gctgcagggc aacctcatcg tggtggggcg gagcagcggc cggctggagg 2220

tgtgggacgc cattgaaggg gtgctgtgct gcagcagcga ggaggtctcc tcaggcatta 2280

ccgctctggt gttcttggac aaaaggattg tggctgcacg gctcaacggt tcccttgatt 2340

tcttctcctt ggggacccac actgccctca gccccctgca gtttagaggg accccagggc 2400

ggggcagttc ccctgcctct ccagtgtaca gcagcagcga cacagtggcc tgtcacctga 2460

cccacacagt gccctgtgca caccaagaac ccatcacagc cctgaaagcc gctgctgggc 2520

gcttggtgac tgggagccaa gaccacacac tgagagtgtt ccgtctggag gactcgtgct 2580

gcctcttcac ccttcagggc cactcagggg ccatcacgac cgtgtacatt gaccagacca 2640

tggtgctggc cagtggagga caagatgggg ccatctgcct gtgggatgta ctgactggca 2700

gccgggtcag ccatgtgttt gctcaccgtg gggatgtcac ctcccttacc tgtaccacct 2760

cctgtgtcat cagcagtggc ctggatgacc tcatcagcat ctgggaccgc agcacaggca 2820

tcaagttcta ctccattcag caggacctgg gctgtggtgc aagcttgggt gtcatctcag 2880

acaacctgct ggtgactggc ggccagggct gtgtctcctt ttgggaccta aactacgggg 2940

acctgttaca gacagtctac ctggggaaga acagtgaggc ccagcctgcc cgccagatcc 3000

tggtgctgga caacgctgcc attgtctgca actttggcag tgagctcagc ctggtgtatg 3060

tgccctctgt gctggagaag ctggactgag cgcagggcct ccttgcccag gcaggaggct 3120

ggggtgctgt gtgggggcca atgcactgaa cctggacttg ggggaaagag ccgagtatct 3180

tccagccgct gcctcctgac tgtaataata ttaaactttt ttaaaaaacc 3230

<210> 25
<211> 2262
<212> DNA
<213> Homo sapiens

<400> 25
ggccgggagt acctgaggag ccggcggcga tgacggcagt ggaggcctag tgggctcggt 60

gcgtgggtcg gcggcggctc ggggtccacc cgcgggctac ggtgcaagcg gggggcccgg 120

ctcccgtcct cccccgcccg gctccgccac tatgattggg tggaagatgg cgctggccag 180

atggaaatcc taatgacagt ctccaaattc gcctccatct gtaccatggg cgccaatgct 240

tcggcattag agaaatagat tggtccagaa cagtttccgg tcaacgagca ttattttgga 300

ttagtcaatt ttgggaatac ctgctactgc aattcagttc ttcaagcact ttatttttgt 360

cgtccgtttc gggaaaaagt tcttgcatat aagagtcaac ctaggaaaaa ggagagcttt 420

cttacatgct tagcagatct cttccacagc atagccactc agaagaaaaa ggttggagta 480

atacctccga agaagttcat cacaagatta cagaaagaaa atgagctttt cgacaactac 540

atgcaacaag atgcccatga attcttaaat tacctactaa atacaattgg tgatatttta 600

caagaagaga gaaagcagga aaaacaaaat ggtcgctaac ctaatgataa tattgataat 660

gaaaataata gcagcacacc agacccaacg tgggttcatg agatttttcg gggaacgtta 720

actaatgaaa ccagacgtct tacttgtgaa actataagca gcaaagatgg agatttttta 780

gacctttctg ttgacgtgga acaaaataca tcaattactc actgcttaag gggtttcagc 840

aacacagaaa ctctatgcag ttaatacaag tattactgtg aagagtgtcg cagcaaacag 900

gaagcacaca aacggatgaa agtttaaaaa ctgcccatga ttctagctgt acacttgaag 960

agatttaaat atatggatca acttcatcga tatacaaaac tctcttaccg ggtggttttt 1020

cctttagaac ttcgtctatt taacacttca ggtgatgcca ccaatccaga cagaatgtac 1080

gaccttgttg ctgttgtggt tcactgtgga agtggtccca atcgaggcca ttatattgcg 1140

atagttaaga gtcatgattt ttggttgttg tttgatgacg acattgtaga aaaaatagat 1200

acacaagcta ttgaagaatt ctacgggttg acatcagata ctcaaagaac tctgagtctg 1260

gttacatcct tttctatcag tctcgggact gaggggggaac cgcgatgaag agatactttc 1320

tgcctcattt cttttctggt tattttggaa aggatcaagc actgattttt caagaaaaga 1380

gaaatgcagg aagctcaggg ggcagtagca ggctttgcac acgataaagc aaaaacgatg 1440

gattgacaag cccttctgat catggtagtt gatttatttg ctcaggtatc atgctgtctg 1500

tacagttcca tacaacaagg aggtgaaatc cataccagct cctcttgtaa aacagccttc 1560

cagtcattga caggcatttc ctctttgcta attgcaccaa taatgctttg aattccttag 1620

gggtgcagta gaaagaatcg gaatctgggc tgtattgata aggagatgat gttgaacgca 1680

ctgcataaat ttgcctggtt cagtatgtat agaagcatat tcagtggtct tttcaagagt 1740

aaaccagaaa tacttttggg cccaacactt gcagttgcct tcctgatgta aaaactaaca 1800

tgctagataa tccagtgtcg ggaagacaaa gatgctttgc ttctctgaag aagcttataa 1860

taatatacag tatatgtata tgtagggagc aattggtcaa aagtggcttt ttgtttccac 1920

aaggggaaag actggctatg taattataat tttttcctta tttattttac ttaaaactgg 1980

tagagtctaa gtattgtatg aagtgcccat gattctgtca gtaaatttga gcatattttt 2040

atcagttaat gtcattttag ctggtccttt tgtttctatt tttaaggcga attttaaatt 2100

atatctgaaa tcagtaagat accttgagaa aaactgcaat gagaggaggt aaatatcctt 2160

ttcaggagga actgatatct ctggctaaat atttgtcctt ttattatggc ttctaaatca 2220

gttattttct tcagctttaa tttcataaaa ttaaaaaact at 2262

<210> 26
<211> 2392
<212> DNA
<213> Homo sapiens

<400> 26
agcggggcag cggctgcgcc ctgcgccggg gcggagccgg gggcgggccg gcggccggca 60

ggcgggggct ggggcccgag gccgggagtg cctgagcgcc ggcggcgacg acggcagcgg 120

cggcccagcg ggctcggtgg ttgggtccgc ggcggctcgg ggtccgcccg cgggctgcgg 180

tgcgagcggg cggcccggct cccctcctcc cccgcccgcc gccgccgctg tgattgggtg 240

gaagatggcg ctggccggat ggaaatccta atgacagtct ccaaattcgc ctccatctgt 300

accatgggcg ccaatgcttc ggcattagag aaagagattg gtccagaaca gtttccggtc 360

aatgagcact attttggatt agtcaatttt gggaatacct gctactgcaa ttcagttctt 420

caagcacttt atttttgtcg tccatttcgg gaaaaagttc ttgcgtataa gagtcaacct 480

aggaaaaagg agagccttct tacatgctta gcagatctct tccatagcat agccactcag 540

aagaaaaagg ttggagtaat acccccctaag aagttcatca caagattacg gaaagaaaat 600

gagctttttg acaactacat gcaacaagat gcccatgaat tcttaaatta cctactaaat 660

acaattgctg atattttaca agaagagaga aagcaggaaa aacaaaatgg tcgtttacct 720

aatggtaata ttgataatga aaataataac agcacaccag acccaacgtg ggttgatgag 780

atttttcagg gaacattaac taatgaaacc agatgtctta cttgtgaaac tataagcagc 840

aaagatgaag atttttttaga cctttctgtt gacgtggaac aaaatacatc aattactcac 900

tgcttaaggg gtttcagcaa cacagaaact ctgtgcagtg aatacaagta ttactgtgaa 960

gagtgtcgca gcaaacagga agcacacaaa cggatgaaag ttaaaaaact gcccatgatt 1020

ctagctctac acctgaagag atttaaatat atggatcaac ttcatcgata tacaaaactc 1080

tcttaccggg tagtttttcc tttagaactt cgtctgttta acacttcagg tgatgccacc 1140

aatccagaca gaatgtacga ccttgttgct gttgtggttc actgtggaag tggtcccaat 1200

cgaggccatt atattgcaat agttaagagt catgattttt ggttgttgtt tgatgacgac 1260

attgtagaaa aaatagatgc acaagctatt gaagaattct acgggttgac atcagatatc 1320

tcaaagaact ctgagtctgg ttacatcctt ttctatcagt ctcgggactg agagggaacc 1380

gtgatgaaga gacactttct gcctcatttc ttctctggtt attttggaaa ggatcaagca 1440

ctgatttttc aagaaaagag aaatgcagga agctcagggg gcagtagcac actttgcaca 1500

cgataaagca aagacgatgg attgacaagc ccttccgatc atggtagttg atttatttgc 1560

tcaggtatca tgctgtctgt acagttccat acaacaagga ggtgaaatca gagataccag 1620

ctcctctttt aaaacagcct tccagtcatt ggcacgcatt ttctctttat taattgcacc 1680

aataatgctt tgaattcctt gggggtgcag tagaaagaat cggaatctgt gccgtattga 1740

taaggagatg atgttgaaca cactgcataa atttgcctgg ttcagtatgt atagaagcat 1800

attcagtggt cttttcaaga gtaaaccaga aatacttttg ggcccaacac ttgcagttgc 1860

cttcctgatg taaaaactaa catgctagat aatccagtgt cgggaagaca aagatgtttt 1920

gcttctctga agaagcttat aataatatac agtatatgta tatgtaggga gcaattggtc 1980

aaaagtggct ttttgtttcc ccaaggggaa agactggctt tgtaattata atttttttcct 2040

tatttatttt acttaaaact ggtagagtct aagtattata tgaagtgccc atgattctgt 2100

cagtaaattt gaacatattt ttattagtta atgtcagttt aagttgtcct tttgtttgtt 2160

tctattttta aggtgaattt taatttctat ctgaaatcag ttaagatacc ttgagaaaaa 2220

ctgcagtgag aggagataaa tatccttttt caggaggaac tgatatctct ggctaaatat 2280

ttgtcctttt attatggttt ctaaatcagt tattttcttc agctttaatt tcataaaatt 2340

aaaaaactat tttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 2392

<210> 27
<211> 2012
<212> DNA
<213> Homo sapiens

<400> 27
gcggctgtcc agtcgtagcc cggccgcccg cgcctgtccg gtccggtccg gccacggagg 60

cagcgcagcg gcgggactcc gagcctaccc cgccgagtga gctgcgccgc accgtgccgt 120

cccacccggc acccaccagt ccgatggggc cgcagcggcg gctgtcccct gccggggccg 180

ccctactctg gggcttcctg ctccagctga cagccgctca ggaagcaatc ttgcatgcgt 240

ctggaaatgg cacaaccaag gactactgca tgctttataa cccttattgg acagctcttc 300

caagtaccct agaaaatgca acttccatta gtttgatgaa tctgacttcc acaccactat 360

gcaacctttc tgatattcct cctgttggca taaagagcaa agcagttgtg gttccatggg 420

gaagctgcca ttttcttgaa aaagccagaa ttgcacagaa aggaggtgct gaagcaatgt 480

tagttgtcaa taacagtgtc ctatttcctc cctcaggtaa cagatctgaa tttcctgatg 540

tgaaaatact gattgcattt ataagctaca aagactttag agatatgaac cagactctag 600

gagataacat tactgtgaaa atgtattctc catcgtggcc taactttgat tatactatgg 660

tggttatttt tgtaattgcg gtgttcactg tggcattagg tggatactgg agtggactag 720

ttgaattgga aaacttgaaa gcagtgacaa ctgaagatag agaaatgagg aaaaagaagg 780

aagaatattt aacttttagt cctcttacag ttgtaatatt tgtggtcatc tgctgtgtta 840

tgatggtctt actttatttc ttctacaaat ggttggttta tgttatgata gcaattttct 900

gcatagcatc agcaatgagt ctgtacaact gtcttgctgc actaattcat aagataccat 960

atggacaatg cacgattgca tgtcgtggca aaaacatgga agtgagactt atttttctct 1020

ctggactgtg catagcagta gctgttgttt gggctgtgtt tcgaaatgaa gacaggtggg 1080

cttggatttt acaggatatc ttggggattg ctttctgtct gaatttaatt aaaacactga 1140

agttgcccaa cttcaagtca tgtgtgatac ttctaggcct tctcctcctc tatgatgtat 1200

tttttgtttt cataacacca ttcatcacaa agaatggtga gagtatcatg gttgaactcg 1260

cagctggacc ttttggaaat aatgaaaagt tgccagtagt catcagagta ccaaaactga 1320

tctatttctc agtaatgagt gtgtgcctca tgcctgtttc aatattgggt tttggagaca 1380

ttattgtacc aggcctgttg attgcatact gtagaagatt tgatgttcag actggttctt 1440

cttacatata ctatgtttcg tctacagttg cctatgctat tggcatgata cttacatttg 1500

ttgttctggt gctgatgaaa aaggggcaac ctgctctcct ctatttagta ccttgcacac 1560

ttattactgc ctcagttgtt gcctggagac gtaaggaaat gaaaaagttc tggaaaggta 1620

acagctatca gatgatggac catttggatt gtgcaacaaa tgaagaaaac cctgtgatat 1680

ctggtgaaca gattgtccag caataatatt atgtggaact gctataatgt gtcattgatt 1740

ttctacaaat agacttcgac tttttaaatt gacttttgaa ttgacaatct gaaagagtct 1800

tcaatgatat gcttgcaaaa atatattttt atgagctggt actgacagtt acatcataaa 1860

taactaaaac gctttgcttt taatgttaaa gttgtgcctt cacattaaat aaaacatatg 1920

gtctgtgtaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 2012

<210> 28
<211> 210
<212> PRT
<213> Homo sapiens

<400> 28

Met Asp Asp Glu Glu Glu Thr Tyr Arg Leu Trp Lys Ile Arg Lys Thr
1 5 10 15

Ile Met Gln Leu Cys His Asp Arg Gly Tyr Leu Val Thr Gln Asp Glu
20 25 30

Leu Asp Gln Thr Leu Glu Glu Phe Lys Ala Gln Phe Gly Asp Lys Pro
35 40 45

Ser Glu Gly Arg Pro Arg Arg Thr Asp Leu Thr Val Leu Val Ala His
50 55 60

Asn Asp Asp Pro Thr Asp Gln Met Phe Val Phe Phe Pro Glu Glu Pro

65 70 75 80

Lys Val Gly Ile Lys Thr Ile Lys Val Tyr Cys Gln Arg Met Gln Glu
85 90 95

Glu Asn Ile Thr Arg Ala Leu Ile Val Val Gln Gln Gly Met Thr Pro
100 105 110

Ser Ala Lys Gln Ser Leu Val Asp Met Ala Pro Lys Tyr Ile Leu Glu
115 120 125

Gln Phe Leu Gln Gln Glu Leu Leu Ile Asn Ile Thr Glu His Glu Leu
130 135 140

Val Pro Glu His Val Val Met Thr Lys Glu Glu Val Thr Glu Leu Leu
145 150 155 160

Ala Arg Tyr Lys Leu Arg Glu Asn Gln Leu Pro Arg Ile Gln Ala Gly
165 170 175

Asp Pro Val Ala Arg Tyr Phe Gly Ile Lys Arg Gly Gln Val Val Lys
180 185 190

Ile Ile Arg Pro Ser Glu Thr Ala Gly Arg Tyr Ile Thr Tyr Arg Leu
195 200 205

Val Gln
210

<210> 29
<211> 285
<212> PRT
<213> Homo sapiens

<400> 29

Met Met Ala Val Asp Ile Glu Tyr Arg Tyr Asn Cys Met Ala Pro Ser
1 5 10 15

Leu Arg Gln Glu Arg Phe Ala Phe Lys Ile Ser Pro Lys Pro Ser Lys
20 25 30

Pro Leu Arg Pro Cys Ile Gln Leu Ser Ser Lys Asn Glu Ala Ser Gly
35 40 45

Met Val Ala Pro Ala Val Gln Glu Lys Lys Val Lys Lys Arg Val Ser
50 55 60

```
Phe Ala Asp Asn Gln Gly Leu Ala Leu Thr Met Val Lys Val Phe Ser
65                  70                  75                  80

Glu Phe Asp Asp Pro Leu Asp Met Pro Phe Asn Ile Thr Glu Leu Leu
                85                  90                  95

Asp Asn Ile Val Ser Leu Thr Thr Ala Glu Ser Glu Ser Phe Val Leu
            100                 105                 110

Asp Phe Ser Gln Pro Ser Ala Asp Tyr Leu Asp Phe Arg Asn Arg Leu
        115                 120                 125

Gln Ala Asp His Val Cys Leu Glu Asn Cys Val Leu Lys Asp Lys Ala
    130                 135                 140

Ile Ala Gly Thr Ala Lys Val Gln Asn Leu Ala Phe Glu Lys Thr Val
145                 150                 155                 160

Lys Ile Arg Met Thr Phe Asp Thr Trp Lys Ser Tyr Thr Asp Phe Pro
                165                 170                 175

Cys Gln Tyr Val Lys Asp Thr Tyr Ala Gly Ser Asp Arg Asp Thr Phe
            180                 185                 190

Ser Phe Asp Ile Ser Leu Pro Glu Lys Ile Gln Ser Tyr Glu Arg Met
        195                 200                 205

Glu Phe Ala Val Tyr Tyr Glu Cys Asn Gly Gln Thr Tyr Trp Asp Ser
    210                 215                 220

Asn Arg Gly Lys Asn Tyr Arg Ile Ile Arg Ala Glu Leu Lys Ser Thr
225                 230                 235                 240

Gln Gly Met Thr Lys Pro His Ser Gly Pro Asp Leu Gly Ile Ser Phe
                245                 250                 255

Asp Gln Phe Gly Ser Pro Arg Cys Ser Tyr Gly Leu Phe Pro Glu Trp
            260                 265                 270

Pro Ser Tyr Leu Gly Tyr Glu Lys Leu Gly Pro Tyr Tyr
        275                 280                 285
```

<210> 30
<211> 317
<212> PRT
<213> Homo sapiens

<400> 30

```
Met Ser Cys Thr Arg Met Ile Gln Val Leu Asp Pro Arg Pro Leu Thr
1               5                  10                  15

Ser Ser Val Met Pro Val Asp Val Ala Met Arg Leu Cys Leu Ala His
            20                  25                  30

Ser Pro Pro Val Lys Ser Phe Leu Gly Pro Tyr Asp Glu Phe Gln Arg
        35                  40                  45

Arg His Phe Val Asn Lys Leu Lys Pro Leu Lys Ser Cys Leu Asn Ile
    50                  55                  60

Lys His Lys Ala Lys Ser Gln Asn Asp Trp Lys Cys Ser His Asn Gln
65                  70                  75                  80

Ala Lys Lys Arg Val Val Phe Ala Asp Ser Lys Gly Leu Ser Leu Thr
                85                  90                  95

Ala Ile His Val Phe Ser Asp Leu Pro Glu Glu Pro Ala Trp Asp Leu
            100                 105                 110

Gln Phe Asp Leu Leu Asp Leu Asn Asp Ile Ser Ser Ala Leu Lys His
        115                 120                 125

His Glu Glu Lys Asn Leu Ile Leu Asp Phe Pro Gln Pro Ser Thr Asp
    130                 135                 140

Tyr Leu Ser Phe Arg Ser His Phe Gln Lys Asn Phe Val Cys Leu Glu
145                 150                 155                 160

Asn Cys Ser Leu Gln Glu Arg Thr Val Thr Gly Thr Val Lys Val Lys
                165                 170                 175

Asn Val Ser Phe Glu Lys Lys Val Gln Ile Arg Ile Thr Phe Asp Ser
            180                 185                 190

Trp Lys Asn Tyr Thr Asp Val Asp Cys Val Tyr Met Lys Asn Val Tyr
        195                 200                 205

Gly Gly Thr Asp Ser Asp Thr Phe Ser Phe Ala Ile Asp Leu Pro Pro
    210                 215                 220

Val Ile Pro Thr Glu Gln Lys Ile Glu Phe Cys Ile Ser Tyr His Ala
225                 230                 235                 240

Asn Gly Gln Val Phe Trp Asp Asn Asn Asp Gly Gln Asn Tyr Arg Ile
```

245 250 255

Val His Val Gln Trp Lys Pro Asp Gly Val Gln Thr Gln Met Ala Pro
260 265 270

Gln Asp Cys Ala Phe His Gln Thr Ser Pro Lys Thr Glu Leu Glu Ser
275 280 285

Thr Ile Phe Gly Ser Pro Arg Leu Ala Ser Gly Leu Phe Pro Glu Trp
290 295 300

Gln Ser Trp Gly Arg Met Glu Asn Leu Ala Ser Tyr Arg
305 310 315

<210> 31
<211> 118
<212> PRT
<213> Homo sapiens

<400> 31

Met Ala Lys Glu Gly Ile Ala Ala Gly Gly Val Met Asp Val Asn Thr
1 5 10 15

Ala Leu Gln Glu Val Leu Lys Thr Ala Leu Ile His Asp Gly Leu Ala
20 25 30

Arg Gly Ile His Glu Ala Ala Glu Ala Leu Asp Lys Cys Gln Ala His
35 40 45

Leu Phe Val Glu Ala Leu Cys His Glu His Gln Ile Asn Leu Ile Lys
50 55 60

Val Asp Asp Asn Lys Lys Leu Gly Glu Arg Ile Gly Leu Cys Lys Ile
65 70 75 80

Asn Arg Glu Gly Lys Pro Cys Lys Val Val Gly Cys Ser Cys Val Val
85 90 95

Val Lys Asp Tyr Gly Lys Glu Ser Gln Ala Lys Asp Val Ile Gln Glu
100 105 110

Tyr Phe Lys Cys Lys Lys
115

<210> 32
<211> 115
<212> PRT
<213> Homo sapiens

<400> 32

Met Ala Glu Glu Gly Ile Thr Ala Gly Gly Ile Met Glu Val Asn Thr
1 5 10 15

Ala Leu Gln Glu Val Leu Lys Thr Ala Leu Val His Asp Gly Pro Ala
20 25 30

Cys Gly Ile Leu Glu Ala Ala Lys Ala Leu Asp Lys Cys Gln Ala His
35 40 45

Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro Val Tyr Val Lys Leu
50 55 60

Val Glu Ala Phe Cys Ala Glu His Arg Thr Asn Arg Leu Lys Arg Gly
65 70 75 80

Glu Ser Gly Cys Lys Val Val Gly Gly Ser Cys Val Glu Val Lys Asp
85 90 95

Ala Gly Lys Glu Cys Gln Ala Lys Asp Val Ile Lys Glu Tyr Phe Lys
100 105 110

Cys Lys Lys
115

<210> 33
<211> 110
<212> PRT
<213> Homo sapiens

<400> 33

Met Ala Lys Glu Gly Ile Ala Ala Gly Gly Val Met Asp Ile Asn Thr
1 5 10 15

Ala Leu Gln Glu Val Leu Lys Thr Thr Leu Ile His Asp Gly Leu Ala
20 25 30

Arg Gly Ile His Glu Ala Ala Lys Pro Leu Asp Lys Gly Gln Ala His
35 40 45

Leu Tyr Val Leu Ala Ser Asn Cys Asp Glu Thr Val Tyr Val Lys Leu
50 55 60

Val Glu Ala Ile Cys Ala Lys His Gln Ile Asn Phe Ile Lys Val Asp
65 70 75 80

```
Asp Asn Lys Lys Val Gly Glu Trp Leu Arg Thr Met Ala Arg Asn Leu
                85                  90                  95

Arg Pro Arg Met Ser Leu Glu Glu Tyr Phe Lys Cys Lys Lys
            100                 105                 110
```

<210> 34
<211> 96
<212> PRT
<213> Homo sapiens

<400> 34

```
Met Ala Gln Glu Gly Ile Ser Ala Gly Gly Val Met Asp Leu Asn Thr
1               5                   10                  15

Ala Leu Gln Glu Val Leu Lys Ala Ala Leu Ile His Asp Gly Leu Ala
            20                  25                  30

Arg Gly Ile Arg Glu Ala Ala Lys Ala Leu Asp Lys Cys Trp Ala His
        35                  40                  45

Pro Cys Ala Ala Pro Asn Ser Cys Leu Cys Gly Trp Leu Val Lys Ala
    50                  55                  60

Leu Val Ala Glu His Gln Ile Thr Leu Ile Lys Val Asp Asp Asn Lys
65                  70                  75                  80

Leu Gly Glu Gly Met Asp His Cys Lys Thr Asp Arg Arg Lys Thr Pro
                85                  90                  95
```

<210> 35
<211> 132
<212> PRT
<213> Homo sapiens

<400> 35

```
Met Ala Glu Glu Gly Ile Ala Ala Gly Gly Val Met Glu Val Asn Thr
1               5                   10                  15

Ala Leu Gln Glu Val Leu Lys Thr Ala Leu Ile His Asp Gly Leu Ala
            20                  25                  30

Arg Gly Ile Arg Glu Ala Ala Lys Val Leu Asp Lys Arg Gln Ala His
        35                  40                  45

Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro Met Tyr Val Lys Leu
    50                  55                  60
```

Val Glu Ala Leu Cys Ala Glu His Gln Ile Asn Leu Ile Lys Val Asp
65 70 75 80

Asp Asn Lys Lys Leu Gly Glu Trp Val Gly Leu Cys Lys Ile Asp Arg
85 90 95

Glu Gly Lys Pro His Lys Val Val Gly Tyr Ser Cys Val Val Val Lys
100 105 110

Asp Tyr Gly Lys Glu Ser Gln Ala Lys Asp Val Ile Glu Glu Tyr Phe
115 120 125

Lys Cys Lys Lys
130

<210> 36
<211> 132
<212> PRT
<213> Homo sapiens

<400> 36

Met Ala Glu Glu Gly Ile Ala Ala Gly Gly Val Met Asp Val Asn Thr
1 5 10 15

Ala Leu Gln Glu Val Leu Lys Thr Ala Leu Ile His Asp Gly Leu Ala
20 25 30

Arg Gly Ile Arg Glu Ala Ala Lys Ala Leu Asp Lys Arg Gln Ala His
35 40 45

Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro Met Tyr Val Lys Leu
50 55 60

Val Glu Ala Leu Cys Ala Glu His Gln Ile Asn Leu Ile Lys Val Asp
65 70 75 80

Asp Asn Lys Lys Leu Gly Glu Trp Val Gly Leu Cys Lys Ile Asp Arg
85 90 95

Glu Gly Lys Pro Arg Lys Val Val Gly Cys Ser Cys Val Val Val Lys
100 105 110

Asp Tyr Gly Lys Glu Ser Gln Ala Lys Asp Val Ile Glu Glu Tyr Phe
115 120 125

Lys Cys Lys Lys
130

<210> 37
<211> 420
<212> PRT
<213> Homo sapiens

<400> 37

Met Thr Met Glu Lys Gly Met Ser Ser Gly Glu Gly Leu Pro Ser Arg
1 5 10 15

Ser Ser Gln Val Ser Ala Gly Lys Ile Thr Ala Lys Glu Leu Glu Thr
20 25 30

Lys Gln Ser Tyr Lys Glu Lys Arg Gly Gly Phe Val Leu Val His Ala
35 40 45

Gly Ala Gly Tyr His Ser Glu Ser Lys Ala Lys Glu Tyr Lys His Val
50 55 60

Cys Lys Arg Ala Cys Gln Lys Ala Ile Glu Lys Leu Gln Ala Gly Ala
65 70 75 80

Leu Ala Thr Asp Ala Val Thr Ala Ala Leu Val Glu Leu Glu Asp Ser
85 90 95

Pro Phe Thr Asn Ala Gly Met Gly Ser Asn Leu Asn Leu Leu Gly Glu
100 105 110

Ile Glu Cys Asp Ala Ser Ile Met Asp Gly Lys Ser Leu Asn Phe Gly
115 120 125

Ala Val Gly Ala Leu Ser Gly Ile Lys Asn Pro Val Ser Val Ala Asn
130 135 140

Arg Leu Leu Cys Glu Gly Gln Lys Gly Lys Leu Ser Ala Gly Arg Ile
145 150 155 160

Pro Pro Cys Phe Leu Val Gly Glu Gly Ala Tyr Arg Trp Ala Val Asp
165 170 175

His Gly Ile Pro Ser Cys Pro Pro Asn Ile Met Thr Thr Arg Phe Ser
180 185 190

Leu Ala Ala Phe Lys Arg Asn Lys Arg Lys Leu Glu Leu Ala Glu Arg
195 200 205

Val Asp Thr Asp Phe Met Gln Leu Lys Lys Arg Arg Gln Ser Ser Glu
210 215 220

Lys Glu Asn Asp Ser Gly Thr Leu Asp Thr Val Gly Ala Val Val Val
225 230 235 240

Asp His Glu Gly Asn Val Ala Ala Ala Val Ser Ser Gly Gly Leu Ala
245 250 255

Leu Lys His Pro Gly Arg Val Gly Gln Ala Ala Leu Tyr Gly Cys Gly
260 265 270

Cys Trp Ala Glu Asn Thr Gly Ala His Asn Pro Tyr Ser Thr Ala Val
275 280 285

Ser Thr Ser Gly Cys Gly Glu His Leu Val Arg Thr Ile Leu Ala Arg
290 295 300

Glu Cys Ser His Ala Leu Gln Ala Glu Asp Ala His Gln Ala Leu Leu
305 310 315 320

Glu Thr Met Gln Asn Lys Phe Ile Ser Ser Pro Phe Leu Ala Ser Glu
325 330 335

Asp Gly Val Leu Gly Gly Val Ile Val Leu Arg Ser Cys Arg Cys Ser
340 345 350

Ala Glu Pro Asp Phe Ser Gln Asn Lys Gln Thr Leu Leu Val Glu Phe
355 360 365

Leu Trp Ser His Thr Thr Glu Ser Met Cys Val Gly Tyr Met Ser Ala
370 375 380

Gln Asp Gly Lys Ala Lys Thr His Ile Ser Arg Leu Pro Pro Gly Ala
385 390 395 400

Val Ala Gly Gln Ser Val Ala Ile Glu Gly Gly Val Cys Arg Leu Glu
405 410 415

Ser Pro Val Asn
420

<210> 38
<211> 496
<212> PRT
<213> Homo sapiens

<400> 38

Met Phe Arg Ser Lys Arg Ser Gly Leu Val Arg Arg Leu Trp Arg Ser

1 5 10 15

Arg Val Val Pro Asn Arg Glu Glu Gly Gly Ser Gly Gly Gly Gly Gly
20 25 30

Gly Asp Glu Asp Gly Ser Leu Gly Ser Arg Ala Glu Pro Ala Pro Arg
35 40 45

Ala Arg Glu Gly Gly Gly Cys Gly Arg Ser Glu Val Arg Pro Val Ala
50 55 60

Pro Arg Arg Pro Arg Asp Ala Val Gly Gln Arg Gly Ala Gln Gly Ala
65 70 75 80

Gly Arg Arg Arg Arg Ala Gly Gly Pro Pro Arg Pro Met Ser Glu Pro
85 90 95

Gly Ala Gly Ala Gly Ser Ser Leu Leu Asp Val Ala Glu Pro Gly Gly
100 105 110

Pro Gly Trp Leu Pro Glu Ser Asp Cys Glu Thr Val Thr Cys Cys Leu
115 120 125

Phe Ser Glu Arg Asp Ala Ala Gly Ala Pro Arg Asp Ala Ser Asp Pro
130 135 140

Leu Ala Gly Ala Ala Leu Glu Pro Ala Gly Gly Gly Arg Ser Arg Glu
145 150 155 160

Ala Arg Ser Arg Leu Leu Leu Leu Glu Gln Glu Leu Lys Thr Val Thr
165 170 175

Tyr Ser Leu Leu Lys Arg Leu Lys Glu Arg Ser Leu Asp Thr Leu Leu
180 185 190

Glu Ala Val Glu Ser Arg Gly Gly Val Pro Gly Gly Cys Val Leu Val
195 200 205

Pro Arg Ala Asp Leu Arg Leu Gly Gly Gln Pro Ala Pro Pro Gln Leu
210 215 220

Leu Leu Gly Arg Leu Phe Arg Trp Pro Asp Leu Gln His Ala Val Glu
225 230 235 240

Leu Lys Pro Leu Cys Gly Cys His Ser Phe Ala Ala Ala Ala Asp Gly
245 250 255

Pro Thr Val Cys Cys Asn Pro Tyr His Phe Ser Arg Leu Cys Gly Pro
260 265 270

Glu Ser Pro Pro Pro Pro Tyr Ser Arg Leu Ser Pro Arg Asp Glu Tyr
275 280 285

Lys Pro Leu Asp Leu Ser Asp Ser Thr Leu Ser Tyr Thr Glu Thr Glu
290 295 300

Ala Thr Asn Ser Leu Ile Thr Ala Pro Gly Glu Phe Ser Asp Ala Ser
305 310 315 320

Met Ser Pro Asp Ala Thr Lys Pro Ser His Trp Cys Ser Val Ala Tyr
325 330 335

Trp Glu His Arg Thr Arg Val Gly Arg Leu Tyr Ala Val Tyr Asp Gln
340 345 350

Ala Val Ser Ile Phe Tyr Asp Leu Pro Gln Gly Ser Gly Phe Cys Leu
355 360 365

Gly Gln Leu Asn Leu Glu Gln Arg Ser Glu Ser Val Arg Arg Thr Arg
370 375 380

Ser Lys Ile Gly Phe Gly Ile Leu Leu Ser Lys Glu Pro Asp Gly Val
385 390 395 400

Trp Ala Tyr Asn Arg Gly Glu His Pro Ile Phe Val Asn Ser Pro Thr
405 410 415

Leu Asp Ala Pro Gly Gly Arg Ala Leu Val Val Arg Lys Val Pro Pro
420 425 430

Gly Tyr Ser Ile Lys Val Phe Asp Phe Glu Arg Ser Gly Leu Gln His
435 440 445

Ala Pro Glu Pro Asp Ala Ala Asp Gly Pro Tyr Asp Pro Asn Ser Val
450 455 460

Arg Ile Ser Phe Ala Lys Gly Trp Gly Pro Cys Tyr Ser Arg Gln Phe
465 470 475 480

Ile Thr Ser Cys Pro Cys Trp Leu Glu Ile Leu Leu Asn Asn Pro Arg
485 490 495

<210> 39

<211> 426
<212> PRT
<213> Homo sapiens

<400> 39

```
Met Phe Arg Thr Lys Arg Ser Ala Leu Val Arg Arg Leu Trp Arg Ser
1               5                  10                  15

Arg Ala Pro Gly Gly Glu Asp Glu Glu Glu Gly Ala Gly Gly Gly Gly
            20                  25                  30

Gly Gly Gly Glu Leu Arg Gly Glu Gly Ala Thr Asp Ser Arg Ala His
        35                  40                  45

Gly Ala Gly Gly Gly Gly Pro Gly Arg Ala Gly Cys Cys Leu Gly Lys
    50                  55                  60

Ala Val Arg Gly Ala Lys Gly His His His Pro His Pro Pro Ala Ala
65                  70                  75                  80

Gly Ala Gly Ala Ala Gly Gly Ala Glu Ala Asp Leu Lys Ala Leu Thr
                85                  90                  95

His Ser Val Leu Lys Lys Leu Lys Glu Arg Gln Leu Glu Leu Leu Leu
            100                 105                 110

Gln Ala Val Glu Ser Arg Gly Gly Thr Arg Thr Ala Cys Leu Leu Leu
        115                 120                 125

Pro Gly Arg Leu Asp Cys Arg Leu Gly Pro Gly Ala Pro Ala Gly Ala
    130                 135                 140

Gln Pro Ala Gln Pro Pro Ser Ser Tyr Ser Leu Pro Leu Leu Leu Cys
145                 150                 155                 160

Lys Val Phe Arg Trp Pro Asp Leu Arg His Ser Ser Glu Val Lys Arg
                165                 170                 175

Leu Cys Cys Cys Glu Ser Tyr Gly Lys Ile Asn Pro Glu Leu Val Cys
            180                 185                 190

Cys Asn Pro His His Leu Ser Arg Leu Cys Glu Leu Glu Ser Pro Pro
        195                 200                 205

Pro Pro Tyr Ser Arg Tyr Pro Met Asp Phe Leu Lys Pro Thr Ala Asp
    210                 215                 220
```

```
Cys Pro Asp Ala Val Pro Ser Ser Ala Glu Thr Gly Gly Thr Asn Tyr
225                 230                 235                 240

Leu Ala Pro Gly Gly Leu Ser Asp Ser Gln Leu Leu Leu Glu Pro Gly
                245                 250                 255

Asp Arg Ser His Trp Cys Val Val Ala Tyr Trp Glu Glu Lys Thr Arg
            260                 265                 270

Val Gly Arg Leu Tyr Cys Val Gln Glu Pro Ser Leu Asp Ile Phe Tyr
        275                 280                 285

Asp Leu Pro Gln Gly Asn Gly Phe Cys Leu Gly Gln Leu Asn Ser Asp
    290                 295                 300

Asn Lys Ser Gln Leu Val Gln Lys Val Arg Ser Lys Ile Gly Cys Gly
305                 310                 315                 320

Ile Gln Leu Thr Arg Glu Val Asp Gly Val Trp Val Tyr Asn Arg Ser
                325                 330                 335

Ser Tyr Pro Ile Phe Ile Lys Ser Ala Thr Leu Asp Asn Pro Asp Ser
            340                 345                 350

Arg Thr Leu Leu Val His Lys Val Phe Pro Gly Phe Ser Ile Lys Ala
        355                 360                 365

Phe Asp Tyr Glu Lys Ala Tyr Ser Leu Gln Arg Pro Asn Asp His Glu
    370                 375                 380

Phe Met Gln Gln Pro Trp Thr Gly Phe Thr Val Gln Ile Ser Phe Val
385                 390                 395                 400

Lys Gly Trp Gly Gln Cys Tyr Thr Arg Gln Phe Ile Ser Ser Cys Pro
                405                 410                 415

Cys Trp Leu Glu Val Ile Phe Asn Ser Arg
            420                 425
```

<210> 40
<211> 367
<212> PRT
<213> Homo sapiens

<400> 40

```
Met Val Met Glu Val Gly Thr Leu Asp Ala Gly Gly Leu Arg Ala Leu
1               5                   10                  15
```

```
Leu Gly Glu Arg Ala Ala Gln Cys Leu Leu Leu Asp Cys Arg Ser Phe
            20                  25                  30

Phe Ala Phe Asn Ala Gly His Ile Ala Gly Ser Val Asn Val Arg Phe
        35                  40                  45

Ser Thr Ile Val Arg Arg Arg Ala Lys Gly Ala Met Gly Leu Glu His
    50                  55                  60

Ile Val Pro Asn Ala Glu Leu Arg Gly Arg Leu Leu Ala Gly Ala Tyr
65                  70                  75                  80

His Ala Val Val Leu Leu Asp Glu Arg Ser Ala Ala Leu Asp Gly Ala
                85                  90                  95

Lys Arg Asp Gly Thr Leu Ala Leu Ala Ala Gly Ala Leu Cys Arg Glu
            100                 105                 110

Ala Arg Ala Ala Gln Val Phe Phe Leu Lys Gly Gly Tyr Glu Ala Phe
        115                 120                 125

Ser Ala Ser Cys Pro Glu Leu Cys Ser Lys Gln Ser Thr Pro Met Gly
    130                 135                 140

Leu Ser Leu Pro Leu Ser Thr Ser Val Pro Asp Ser Ala Glu Ser Gly
145                 150                 155                 160

Cys Ser Ser Cys Ser Thr Pro Leu Tyr Asp Gln Gly Gly Pro Val Glu
                165                 170                 175

Ile Leu Pro Phe Leu Tyr Leu Gly Ser Ala Tyr His Ala Ser Arg Lys
            180                 185                 190

Asp Met Leu Asp Ala Leu Gly Ile Thr Ala Leu Ile Asn Val Ser Ala
        195                 200                 205

Asn Cys Pro Asn His Phe Glu Gly His Tyr Gln Tyr Lys Ser Ile Pro
    210                 215                 220

Val Glu Asp Asn His Lys Ala Asp Ile Ser Ser Trp Phe Asn Glu Ala
225                 230                 235                 240

Ile Asp Phe Ile Asp Ser Ile Lys Asn Ala Gly Gly Arg Val Phe Val
                245                 250                 255

His Cys Gln Ala Gly Ile Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr
```

260 265 270

Leu Met Arg Thr Asn Arg Val Lys Leu Asp Glu Ala Phe Glu Phe Val
275 280 285

Lys Gln Arg Arg Ser Ile Ile Ser Pro Asn Phe Ser Phe Met Gly Gln
290 295 300

Leu Leu Gln Phe Glu Ser Gln Val Leu Ala Pro His Cys Ser Ala Glu
305 310 315 320

Ala Gly Ser Pro Ala Met Ala Val Leu Asp Arg Gly Thr Ser Thr Thr
325 330 335

Thr Val Phe Asn Phe Pro Val Ser Ile Pro Val His Ser Thr Asn Ser
340 345 350

Ala Leu Ser Tyr Leu Gln Ser Pro Ile Thr Thr Ser Pro Ser Cys
355 360 365

<210> 41
<211> 314
<212> PRT
<213> Homo sapiens

<400> 41

Met Gly Leu Glu Ala Ala Arg Glu Leu Glu Cys Ala Ala Leu Gly Thr
1 5 10 15

Leu Leu Arg Asp Pro Arg Glu Ala Glu Arg Thr Leu Leu Leu Asp Cys
20 25 30

Arg Pro Phe Leu Ala Phe Cys Arg Arg His Val Arg Ala Ala Arg Pro
35 40 45

Val Pro Trp Asn Ala Leu Leu Arg Arg Arg Ala Arg Gly Pro Pro Ala
50 55 60

Ala Val Leu Ala Cys Leu Leu Pro Asp Arg Ala Leu Arg Thr Arg Leu
65 70 75 80

Val Arg Gly Glu Leu Ala Arg Ala Val Val Leu Asp Glu Gly Ser Ala
85 90 95

Ser Val Ala Glu Leu Arg Pro Asp Ser Pro Ala His Val Leu Leu Ala
100 105 110

Ala Leu Leu His Glu Thr Arg Ala Gly Pro Thr Ala Val Tyr Phe Leu
115 120 125

Arg Gly Gly Phe Asp Gly Phe Gln Gly Cys Cys Pro Asp Leu Cys Ser
130 135 140

Glu Ala Pro Ala Pro Ala Leu Pro Pro Thr Gly Asp Lys Thr Ser Arg
145 150 155 160

Ser Asp Ser Arg Ala Pro Val Tyr Asp Gln Gly Gly Pro Val Glu Ile
165 170 175

Leu Pro Tyr Leu Phe Leu Gly Ser Cys Ser His Ser Ser Asp Leu Gln
180 185 190

Gly Leu Gln Ala Cys Gly Ile Thr Ala Val Leu Asn Val Ser Ala Ser
195 200 205

Cys Pro Asn His Phe Glu Gly Leu Phe Arg Tyr Lys Ser Ile Pro Val
210 215 220

Glu Asp Asn Gln Met Val Glu Ile Ser Ala Trp Phe Gln Glu Ala Ile
225 230 235 240

Gly Phe Ile Asp Trp Val Lys Asn Ser Gly Gly Arg Val Leu Val His
245 250 255

Cys Gln Ala Gly Ile Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr Leu
260 265 270

Met Gln Ser Arg Arg Val Arg Leu Asp Glu Ala Phe Asp Phe Val Lys
275 280 285

Gln Arg Arg Gly Val Ile Ser Pro Asn Phe Ser Phe Met Gly Gln Leu
290 295 300

Leu Gln Phe Glu Thr Gln Val Leu Cys His
305 310

<210> 42
<211> 384
<212> PRT
<213> Homo sapiens

<400> 42

Met Lys Val Thr Ser Leu Asp Gly Arg Gln Leu Arg Lys Met Leu Arg
1 5 10 15

Lys Glu Ala Ala Ala Arg Cys Val Val Leu Asp Cys Arg Pro Tyr Leu
20 25 30

Ala Phe Ala Ala Ser Asn Val Arg Gly Ser Leu Asn Val Asn Leu Asn
35 40 45

Ser Val Val Leu Arg Arg Ala Arg Gly Gly Ala Val Ser Ala Arg Tyr
50 55 60

Val Leu Pro Asp Glu Ala Ala Arg Ala Arg Leu Leu Gln Glu Gly Gly
65 70 75 80

Gly Gly Val Ala Ala Val Val Val Leu Asp Gln Gly Ser Arg His Trp
85 90 95

Gln Lys Leu Arg Glu Glu Ser Ala Ala Arg Val Val Leu Thr Ser Leu
100 105 110

Leu Ala Cys Leu Pro Ala Gly Pro Arg Val Tyr Phe Leu Lys Gly Gly
115 120 125

Tyr Glu Thr Phe Tyr Ser Glu Tyr Pro Glu Cys Cys Val Asp Val Lys
130 135 140

Pro Ile Ser Gln Glu Lys Ile Glu Ser Glu Arg Ala Leu Ile Ser Gln
145 150 155 160

Cys Gly Lys Pro Val Val Asn Val Ser Tyr Arg Pro Ala Tyr Asp Gln
165 170 175

Gly Gly Pro Val Glu Ile Leu Pro Phe Leu Tyr Leu Gly Ser Ala Tyr
180 185 190

His Ala Ser Lys Cys Glu Phe Leu Ala Asn Leu His Ile Thr Ala Leu
195 200 205

Leu Asn Val Ser Arg Arg Thr Ser Glu Ala Cys Met Thr His Leu His
210 215 220

Tyr Lys Trp Ile Pro Val Glu Asp Ser His Thr Ala Asp Ile Ser Ser
225 230 235 240

His Phe Gln Glu Ala Ile Asp Phe Ile Asp Cys Val Arg Glu Lys Gly
245 250 255

Gly Lys Val Leu Val His Cys Glu Ala Gly Ile Ser Arg Ser Pro Thr

260 265 270

Ile Cys Met Ala Tyr Leu Met Lys Thr Lys Gln Phe Arg Leu Lys Glu
275 280 285

Ala Phe Asp Tyr Ile Lys Gln Arg Arg Ser Met Val Ser Pro Asn Phe
290 295 300

Gly Phe Met Gly Gln Leu Leu Gln Tyr Glu Ser Glu Ile Leu Pro Ser
305 310 315 320

Thr Pro Asn Pro Gln Pro Pro Ser Cys Gln Gly Glu Ala Ala Gly Ser
325 330 335

Ser Leu Ile Gly His Leu Gln Thr Leu Ser Pro Asp Met Gln Gly Ala
340 345 350

Tyr Cys Thr Phe Pro Ala Ser Val Leu Ala Pro Val Pro Thr His Ser
355 360 365

Thr Val Ser Glu Leu Ser Arg Ser Pro Val Ala Thr Ala Thr Ser Cys
370 375 380

<210> 43
<211> 381
<212> PRT
<213> Homo sapiens

<400> 43

Met Ile Asp Thr Leu Arg Pro Val Pro Phe Ala Ser Glu Met Ala Ile
1 5 10 15

Ser Lys Thr Val Ala Trp Leu Asn Glu Gln Leu Glu Leu Gly Asn Glu
20 25 30

Arg Leu Leu Leu Met Asp Cys Arg Pro Gln Glu Leu Tyr Glu Ser Ser
35 40 45

His Ile Glu Ser Ala Ile Asn Val Ala Ile Pro Gly Ile Met Leu Arg
50 55 60

Arg Leu Gln Lys Gly Asn Leu Pro Val Arg Ala Leu Phe Thr Arg Gly
65 70 75 80

Glu Asp Arg Asp Arg Phe Thr Arg Arg Cys Gly Thr Asp Thr Val Val
85 90 95

Leu Tyr Asp Glu Ser Ser Ser Asp Trp Asn Glu Asn Thr Gly Gly Glu
100 105 110

Ser Leu Leu Gly Leu Leu Leu Lys Lys Leu Lys Asp Glu Gly Cys Arg
115 120 125

Ala Phe Tyr Leu Glu Gly Gly Phe Ser Lys Phe Gln Ala Glu Phe Ser
130 135 140

Leu His Cys Glu Thr Asn Leu Asp Gly Ser Cys Ser Ser Ser Ser Pro
145 150 155 160

Pro Leu Pro Val Leu Gly Leu Gly Gly Leu Arg Ile Ser Ser Asp Ser
165 170 175

Ser Ser Asp Ile Glu Ser Asp Leu Asp Arg Asp Pro Asn Ser Ala Thr
180 185 190

Asp Ser Asp Gly Ser Pro Leu Ser Asn Ser Gln Pro Ser Phe Pro Val
195 200 205

Glu Ile Leu Pro Phe Leu Tyr Leu Gly Cys Ala Lys Asp Ser Thr Asn
210 215 220

Leu Asp Val Leu Glu Glu Phe Gly Ile Lys Tyr Ile Leu Asn Val Thr
225 230 235 240

Pro Asn Leu Pro Asn Leu Phe Glu Asn Ala Gly Glu Phe Lys Tyr Lys
245 250 255

Gln Ile Pro Ile Ser Asp His Trp Ser Gln Asn Leu Ser Gln Phe Phe
260 265 270

Pro Glu Ala Ile Ser Phe Ile Asp Glu Ala Arg Gly Lys Asn Cys Gly
275 280 285

Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Val Thr Val Thr
290 295 300

Val Ala Tyr Leu Met Gln Lys Leu Asn Leu Ser Met Asn Asp Ala Tyr
305 310 315 320

Asp Ile Val Lys Met Lys Lys Ser Asn Ile Ser Pro Asn Phe Asn Phe
325 330 335

Met Gly Gln Leu Leu Asp Phe Glu Arg Thr Leu Gly Leu Ser Ser Pro
340 345 350

Cys Asp Asn Arg Val Pro Ala Gln Gln Leu Tyr Phe Thr Thr Pro Ser
355 360 365

Asn Gln Asn Val Tyr Gln Val Asp Ser Leu Gln Ser Thr
370 375 380

<210> 44
<211> 419
<212> PRT
<213> Homo sapiens

<400> 44

Met Lys Asn Gln Leu Arg Gly Pro Pro Ala Arg Ala His Met Ser Thr
1 5 10 15

Ser Gly Ala Ala Ala Ala Gly Gly Thr Arg Ala Gly Ser Glu Pro Gly
20 25 30

Ala Gly Ser Gly Ser Gly Ala Gly Thr Gly Ala Gly Ala Ala Thr Gly
35 40 45

Ala Gly Ala Met Pro Cys Lys Ser Ala Glu Trp Leu Gln Glu Glu Leu
50 55 60

Glu Ala Arg Gly Gly Ala Ser Leu Leu Leu Leu Asp Cys Arg Pro His
65 70 75 80

Glu Leu Phe Glu Ser Ser His Ile Glu Thr Ala Ile Asn Leu Ala Ile
85 90 95

Pro Gly Leu Met Leu Arg Arg Leu Arg Lys Gly Asn Leu Pro Ile Arg
100 105 110

Ser Ile Ile Pro Asn His Ala Asp Lys Glu Arg Phe Ala Thr Arg Cys
115 120 125

Lys Ala Ala Thr Val Leu Leu Tyr Asp Glu Ala Thr Ala Glu Trp Gln
130 135 140

Pro Glu Pro Gly Ala Pro Ala Ser Val Leu Gly Leu Leu Leu Gln Lys
145 150 155 160

Leu Arg Asp Asp Gly Cys Gln Ala Tyr Tyr Leu Gln Gly Gly Phe Asn
165 170 175

Lys Phe Gln Thr Glu Tyr Ser Glu His Cys Glu Thr Asn Val Asp Ser

180 185 190

Ser Ser Ser Pro Ser Ser Ser Pro Pro Thr Ser Val Leu Gly Leu Gly
195 200 205

Gly Leu Arg Ile Ser Ser Asp Cys Ser Asp Gly Glu Ser Asp Arg Glu
210 215 220

Leu Pro Ser Ser Ala Thr Glu Ser Asp Gly Ser Pro Val Pro Ser Ser
225 230 235 240

Gln Pro Ala Phe Pro Val Gln Ile Leu Pro Tyr Leu Tyr Leu Gly Cys
245 250 255

Ala Lys Asp Ser Thr Asn Leu Asp Val Leu Gly Lys Tyr Gly Ile Lys
260 265 270

Tyr Ile Leu Asn Val Thr Pro Asn Leu Pro Asn Ala Phe Glu His Gly
275 280 285

Gly Glu Phe Thr Tyr Lys Gln Ile Pro Ile Ser Asp His Trp Ser Gln
290 295 300

Asn Leu Ser Gln Phe Phe Pro Glu Ala Ile Ser Phe Ile Asp Glu Ala
305 310 315 320

Arg Ser Lys Lys Cys Gly Val Leu Val His Cys Leu Ala Gly Ile Ser
325 330 335

Arg Ser Val Thr Val Thr Val Ala Tyr Leu Met Gln Lys Met Asn Leu
340 345 350

Ser Leu Asn Asp Ala Tyr Asp Phe Val Lys Arg Lys Lys Ser Asn Ile
355 360 365

Ser Pro Asn Phe Asn Phe Met Gly Gln Leu Leu Asp Phe Glu Arg Thr
370 375 380

Leu Gly Leu Ser Ser Pro Cys Asp Asn His Ala Ser Ser Glu Gln Leu
385 390 395 400

Tyr Phe Ser Thr Pro Thr Asn His Asn Leu Phe Pro Leu Asn Thr Leu
405 410 415

Glu Ser Thr

<210> 45
<211> 625
<212> PRT
<213> Homo sapiens

<400> 45

```
Met Ala Gly Asp Arg Leu Pro Arg Lys Val Met Asp Ala Lys Lys Leu
1               5                   10                  15

Ala Ser Leu Leu Arg Gly Gly Pro Gly Gly Pro Leu Val Ile Asp Ser
            20                  25                  30

Arg Ser Phe Val Glu Tyr Asn Ser Trp His Val Leu Ser Ser Val Asn
        35                  40                  45

Ile Cys Cys Ser Lys Leu Val Lys Arg Arg Leu Gln Gln Gly Lys Val
    50                  55                  60

Thr Ile Ala Glu Leu Ile Gln Pro Ala Ala Arg Ser Gln Val Glu Ala
65                  70                  75                  80

Thr Glu Pro Gln Asp Val Val Val Tyr Asp Gln Ser Thr Arg Asp Ala
                85                  90                  95

Ser Val Leu Ala Ala Asp Ser Phe Leu Ser Ile Leu Leu Ser Lys Leu
            100                 105                 110

Asp Gly Cys Phe Asp Ser Val Ala Ile Leu Thr Gly Gly Phe Ala Thr
        115                 120                 125

Phe Ser Ser Cys Phe Pro Gly Leu Cys Glu Gly Lys Pro Ala Ala Leu
    130                 135                 140

Leu Pro Met Ser Leu Ser Gln Pro Cys Leu Pro Val Pro Ser Val Gly
145                 150                 155                 160

Leu Thr Arg Ile Leu Pro His Leu Tyr Leu Gly Ser Gln Lys Asp Val
                165                 170                 175

Leu Asn Lys Asp Leu Met Thr Gln Asn Gly Ile Ser Tyr Val Leu Asn
            180                 185                 190

Ala Ser Asn Ser Cys Pro Lys Pro Asp Phe Ile Cys Glu Ser Arg Phe
        195                 200                 205

Met Arg Val Pro Ile Asn Asp Asn Tyr Cys Glu Lys Leu Leu Pro Trp
    210                 215                 220
```

```
Leu Asp Lys Ser Ile Glu Phe Ile Asp Lys Ala Lys Leu Ser Ser Cys
225                 230                 235                 240

Gln Val Ile Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala Thr Ile
                245                 250                 255

Ala Ile Ala Tyr Ile Met Lys Thr Met Gly Met Ser Ser Asp Asp Ala
            260                 265                 270

Tyr Arg Phe Val Lys Asp Arg Arg Pro Ser Ile Ser Pro Asn Phe Asn
        275                 280                 285

Phe Leu Gly Gln Leu Leu Glu Tyr Glu Arg Thr Leu Lys Leu Leu Ala
    290                 295                 300

Ala Leu Gln Gly Asp Pro Gly Thr Pro Ser Gly Thr Pro Glu Pro Pro
305                 310                 315                 320

Pro Ser Pro Ala Ala Gly Ala Pro Leu Pro Arg Leu Pro Pro Pro Thr
                325                 330                 335

Ser Glu Ser Ala Ala Thr Gly Asn Ala Ala Ala Arg Glu Gly Gly Leu
            340                 345                 350

Ser Ala Gly Gly Glu Pro Pro Ala Pro Pro Thr Pro Pro Ala Thr Ser
        355                 360                 365

Ala Leu Gln Gln Gly Leu Arg Gly Leu His Leu Ser Ser Asp Arg Leu
    370                 375                 380

Gln Asp Thr Asn Arg Leu Lys Arg Ser Phe Ser Leu Asp Ile Lys Ser
385                 390                 395                 400

Ala Tyr Ala Pro Ser Arg Arg Pro Asp Gly Pro Gly Pro Pro Asp Pro
                405                 410                 415

Gly Glu Ala Pro Lys Leu Cys Lys Leu Asp Ser Pro Ser Gly Ala Ala
            420                 425                 430

Leu Gly Leu Ser Ser Pro Ser Pro Asp Ser Pro Asp Ala Ala Pro Glu
        435                 440                 445

Ala Arg Pro Arg Pro Arg Arg Arg Pro Arg Pro Pro Ala Gly Ser Pro
    450                 455                 460
```

Ala Arg Ser Pro Ala His Ser Leu Gly Leu Asn Phe Gly Asp Ala Ala
465 470 475 480

Arg Gln Thr Pro Arg His Gly Leu Ser Ala Leu Ser Ala Pro Gly Leu
485 490 495

Pro Gly Pro Gly Gln Pro Ala Gly Pro Gly Ala Trp Ala Pro Pro Leu
500 505 510

Asp Ser Pro Gly Thr Pro Ser Pro Asp Gly Pro Trp Cys Phe Ser Pro
515 520 525

Glu Gly Ala Gln Gly Ala Gly Gly Val Leu Phe Ala Pro Phe Gly Arg
530 535 540

Ala Gly Ala Pro Gly Pro Gly Gly Gly Ser Asp Leu Arg Arg Arg Glu
545 550 555 560

Ala Ala Arg Ala Glu Pro Arg Asp Ala Arg Thr Gly Trp Pro Glu Glu
565 570 575

Pro Ala Pro Glu Thr Gln Phe Lys Arg Arg Ser Cys Gln Met Glu Phe
580 585 590

Glu Glu Gly Met Val Glu Gly Arg Ala Arg Gly Glu Glu Leu Ala Ala
595 600 605

Leu Gly Lys Gln Ala Ser Phe Ser Gly Ser Val Glu Val Ile Glu Val
610 615 620

Ser
625

<210> 46
<211> 384
<212> PRT
<213> Homo sapiens

<400> 46

Met Glu Gly Leu Gly Arg Ser Cys Leu Trp Leu Arg Arg Glu Leu Ser
1 5 10 15

Pro Pro Arg Pro Arg Leu Leu Leu Leu Asp Cys Arg Ser Arg Glu Leu
20 25 30

Tyr Glu Ser Ala Arg Ile Gly Gly Ala Leu Ser Val Ala Leu Pro Ala
35 40 45

Leu Leu Leu Arg Arg Leu Arg Arg Gly Ser Leu Ser Val Arg Ala Leu
50 55 60

Leu Pro Gly Pro Pro Leu Gln Pro Pro Pro Pro Ala Pro Val Leu Leu
65 70 75 80

Tyr Asp Gln Gly Gly Gly Arg Arg Arg Arg Gly Glu Ala Glu Ala Glu
85 90 95

Ala Glu Glu Trp Glu Ala Glu Ser Val Leu Gly Thr Leu Leu Gln Lys
100 105 110

Leu Arg Glu Glu Gly Tyr Leu Ala Tyr Tyr Leu Gln Gly Gly Phe Ser
115 120 125

Arg Phe Gln Ala Glu Cys Pro His Leu Cys Glu Thr Ser Leu Ala Gly
130 135 140

Arg Ala Gly Ser Ser Met Ala Pro Val Pro Gly Pro Val Pro Val Val
145 150 155 160

Gly Leu Gly Ser Leu Cys Leu Gly Ser Asp Cys Ser Asp Ala Glu Ser
165 170 175

Glu Ala Asp Arg Asp Ser Met Ser Cys Gly Leu Asp Ser Glu Gly Ala
180 185 190

Thr Pro Pro Pro Val Gly Leu Arg Ala Ser Phe Pro Val Gln Ile Leu
195 200 205

Pro Asn Leu Tyr Leu Gly Ser Ala Arg Asp Ser Ala Asn Leu Glu Ser
210 215 220

Leu Ala Lys Leu Gly Ile Arg Tyr Ile Leu Asn Val Thr Pro Asn Leu
225 230 235 240

Pro Asn Phe Phe Glu Lys Asn Gly Asp Phe His Tyr Lys Gln Ile Pro
245 250 255

Ile Ser Asp His Trp Ser Gln Asn Leu Ser Arg Phe Phe Pro Glu Ala
260 265 270

Ile Glu Phe Ile Asp Glu Ala Leu Ser Gln Asn Cys Gly Val Leu Val
275 280 285

His Cys Leu Ala Gly Val Ser Arg Ser Val Thr Val Thr Val Ala Tyr

290 295 300

Leu Met Gln Lys Leu His Leu Ser Leu Asn Asp Ala Tyr Asp Leu Val
305 310 315 320

Lys Arg Lys Lys Ser Asn Ile Ser Pro Asn Phe Asn Phe Met Gly Gln
325 330 335

Leu Leu Asp Phe Glu Arg Ser Leu Arg Leu Glu Glu Arg His Ser Gln
340 345 350

Glu Gln Gly Ser Gly Gly Gln Ala Ser Ala Ala Ser Asn Pro Pro Ser
355 360 365

Phe Phe Thr Thr Pro Thr Ser Asp Gly Ala Phe Glu Leu Ala Pro Thr
370 375 380

<210> 47
<211> 303
<212> PRT
<213> Homo sapiens

<400> 47

Met Gly Arg Lys Val His Ser Asn Gly Ser Gln Phe Ala Glu His Ser
1 5 10 15

Arg Ser Pro Arg Arg Thr Gly Arg Asp Cys Lys Pro Val Arg Ala Pro
20 25 30

Ser Met Ala Leu Gly Val Ser Gln Leu Ala Gly Arg Ser Arg Cys Leu
35 40 45

Cys Ser Glu Ser Gln Gly Gly Tyr Glu Arg Phe Ser Ser Glu Tyr Pro
50 55 60

Glu Phe Cys Ser Lys Thr Lys Ala Leu Ala Ala Ile Pro Pro Pro Val
65 70 75 80

Pro Pro Ser Ala Thr Glu Pro Leu Asp Leu Gly Cys Ser Ser Cys Gly
85 90 95

Thr Pro Leu His Asp Gln Gly Gly Pro Val Glu Ile Leu Pro Phe Leu
100 105 110

Tyr Leu Gly Ser Ala Tyr His Ala Ala Arg Arg Asp Met Leu Asp Ala
115 120 125

Leu Gly Ile Thr Ala Leu Leu Asn Val Ser Ser Asp Cys Pro Asn His
130 135 140

Phe Glu Gly His Tyr Gln Tyr Lys Cys Ile Pro Val Glu Asp Asn His
145 150 155 160

Lys Ala Asp Ile Ser Ser Trp Phe Met Glu Ala Ile Glu Tyr Ile Asp
165 170 175

Ala Val Lys Asp Cys Arg Gly Arg Val Leu Val His Cys Gln Ala Gly
180 185 190

Ile Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr Leu Met Met Lys Lys
195 200 205

Arg Val Arg Leu Glu Glu Ala Phe Glu Phe Val Lys Gln Arg Arg Ser
210 215 220

Ile Ile Ser Pro Asn Phe Ser Phe Met Gly Gln Leu Leu Gln Phe Glu
225 230 235 240

Ser Gln Val Leu Ala Thr Ser Cys Ala Ala Glu Ala Ala Ser Pro Ser
245 250 255

Gly Pro Leu Arg Glu Arg Gly Lys Thr Pro Ala Thr Pro Thr Ser Gln
260 265 270

Phe Val Phe Ser Phe Pro Val Ser Val Gly Val His Ser Ala Pro Ser
275 280 285

Ser Leu Pro Tyr Leu His Ser Pro Ile Thr Thr Ser Pro Ser Cys
290 295 300

<210> 48
<211> 330
<212> PRT
<213> Homo sapiens

<400> 48

Met Ala Ala Val Asp Ser Phe Tyr Leu Leu Tyr Arg Glu Ile Ala Arg
1 5 10 15

Ser Cys Asn Cys Tyr Met Glu Ala Leu Ala Leu Val Gly Ala Trp Tyr
20 25 30

Thr Ala Arg Lys Ser Ile Thr Val Ile Cys Asp Phe Tyr Ser Leu Ile
35 40 45

```
Arg Leu His Phe Ile Pro Arg Leu Gly Ser Arg Ala Asp Leu Ile Lys
    50                  55                  60

Gln Tyr Gly Arg Trp Ala Val Val Ser Gly Ala Thr Asp Gly Ile Gly
65                  70                  75                  80

Lys Ala Tyr Ala Glu Glu Leu Ala Ser Arg Gly Leu Asn Ile Ile Leu
                85                  90                  95

Ile Ser Arg Asn Glu Glu Lys Leu Gln Val Val Ala Lys Asp Ile Ala
            100                 105                 110

Asp Thr Tyr Lys Val Glu Thr Asp Ile Ile Val Ala Asp Phe Ser Ser
        115                 120                 125

Gly Arg Glu Ile Tyr Leu Pro Ile Arg Glu Ala Leu Lys Asp Lys Asp
    130                 135                 140

Val Gly Ile Leu Val Asn Asn Val Gly Val Phe Tyr Pro Tyr Pro Gln
145                 150                 155                 160

Tyr Phe Thr Gln Leu Ser Glu Asp Lys Leu Trp Asp Ile Ile Asn Val
                165                 170                 175

Asn Ile Ala Ala Ala Ser Leu Met Val His Val Val Leu Pro Gly Met
            180                 185                 190

Val Glu Arg Lys Lys Gly Ala Ile Val Thr Ile Ser Ser Gly Ser Cys
        195                 200                 205

Cys Lys Pro Thr Pro Gln Leu Ala Ala Phe Ser Ala Ser Lys Ala Tyr
    210                 215                 220

Leu Asp His Phe Ser Arg Ala Leu Gln Tyr Glu Tyr Ala Ser Lys Gly
225                 230                 235                 240

Ile Phe Val Gln Ser Leu Ile Pro Phe Tyr Val Ala Thr Ser Met Thr
                245                 250                 255

Ala Pro Ser Asn Phe Leu His Arg Cys Ser Trp Leu Val Pro Ser Pro
            260                 265                 270

Lys Val Tyr Ala His His Ala Val Ser Thr Leu Gly Ile Ser Lys Arg
        275                 280                 285

Thr Thr Gly Tyr Trp Ser His Ser Ile Gln Phe Leu Phe Ala Gln Tyr
```

290 295 300

Met Pro Glu Trp Leu Trp Val Trp Gly Ala Asn Ile Leu Asn Arg Ser
305 310 315 320

Leu Arg Lys Glu Ala Leu Cys Cys Thr Ala
325 330

<210> 49
<211> 668
<212> PRT
<213> Homo sapiens

<400> 49

Met Ala Glu Pro Leu Leu Arg Lys Thr Phe Ser Arg Leu Arg Gly Arg
1 5 10 15

Glu Lys Leu Pro Arg Lys Lys Ser Asp Ala Lys Glu Arg Gly Pro Gly
20 25 30

Val Pro Gly Thr Gly Glu Pro Ala Gly Glu Ile Trp Tyr Asn Pro Ile
35 40 45

Pro Glu Glu Asp Pro Arg Pro Pro Ala Pro Glu Pro Pro Gly Pro Gln
50 55 60

Pro Gly Ser Ala Glu Ser Glu Gly Leu Ala Pro Gln Gly Ala Ala Pro
65 70 75 80

Ala Ser Pro Pro Thr Lys Ala Ser Arg Thr Lys Ser Pro Gly Pro Ala
85 90 95

Arg Arg Leu Ser Ile Lys Met Lys Lys Leu Pro Glu Leu Arg Arg Arg
100 105 110

Leu Ser Leu Arg Gly Pro Arg Ala Gly Arg Glu Arg Glu Arg Ala Ala
115 120 125

Pro Ala Gly Ser Val Ile Ser Arg Tyr His Leu Asp Ser Ser Val Gly
130 135 140

Gly Pro Gly Pro Ala Ala Gly Pro Gly Gly Thr Arg Ser Pro Arg Ala
145 150 155 160

Gly Tyr Leu Ser Asp Gly Asp Ser Pro Glu Arg Pro Ala Gly Pro Pro
165 170 175

```
Ser Pro Thr Ser Phe Arg Pro Tyr Glu Val Gly Pro Ala Ala Arg Ala
            180                 185                 190

Pro Pro Ala Ala Leu Trp Gly Arg Leu Ser Leu His Leu Tyr Gly Leu
        195                 200                 205

Gly Gly Leu Arg Pro Ala Pro Gly Ala Thr Pro Arg Asp Leu Cys Cys
    210                 215                 220

Leu Leu Gln Val Asp Gly Glu Ala Arg Ala Arg Thr Gly Pro Leu Arg
225                 230                 235                 240

Gly Gly Pro Asp Phe Leu Arg Leu Asp His Thr Phe His Leu Glu Leu
                245                 250                 255

Glu Ala Ala Arg Leu Leu Arg Ala Leu Val Leu Ala Trp Asp Pro Gly
            260                 265                 270

Val Arg Arg His Arg Pro Cys Ala Gln Gly Thr Val Leu Leu Pro Thr
        275                 280                 285

Val Phe Arg Gly Cys Gln Ala Gln Gln Leu Ala Val Arg Leu Glu Pro
    290                 295                 300

Gln Gly Leu Leu Tyr Ala Lys Leu Thr Leu Ser Glu Gln Gln Glu Ala
305                 310                 315                 320

Pro Ala Thr Ala Glu Pro Arg Val Phe Gly Leu Pro Leu Pro Leu Leu
                325                 330                 335

Val Glu Arg Glu Arg Pro Pro Gly Gln Val Pro Leu Ile Ile Gln Lys
            340                 345                 350

Cys Val Gly Gln Ile Glu Arg Arg Gly Leu Arg Val Val Gly Leu Tyr
        355                 360                 365

Arg Leu Cys Gly Ser Ala Ala Val Lys Lys Glu Leu Arg Asp Ala Phe
    370                 375                 380

Glu Arg Asp Ser Ala Ala Val Cys Leu Ser Glu Asp Leu Tyr Pro Asp
385                 390                 395                 400

Ile Asn Val Ile Thr Gly Ile Leu Lys Asp Tyr Leu Arg Glu Leu Pro
                405                 410                 415

Thr Pro Leu Ile Thr Gln Pro Leu Tyr Lys Val Val Leu Glu Ala Met
            420                 425                 430
```

```
Ala Arg Asp Pro Pro Asn Arg Val Pro Pro Thr Thr Glu Gly Thr Arg
        435                 440                 445

Gly Leu Leu Ser Cys Leu Pro Asp Val Glu Arg Ala Thr Leu Thr Leu
    450                 455                 460

Leu Leu Asp His Leu Arg Leu Val Ser Ser Phe His Ala Tyr Asn Arg
465                 470                 475                 480

Met Thr Pro Gln Asn Leu Ala Val Cys Phe Gly Pro Val Leu Leu Pro
                485                 490                 495

Ala Arg Gln Ala Pro Thr Arg Pro Arg Ala Arg Ser Ser Gly Pro Gly
            500                 505                 510

Leu Ala Ser Ala Val Asp Phe Lys His His Ile Glu Val Leu His Tyr
        515                 520                 525

Leu Leu Gln Ser Trp Pro Asp Pro Arg Leu Pro Arg Gln Ser Pro Asp
    530                 535                 540

Val Ala Pro Tyr Leu Arg Pro Lys Arg Gln Pro Pro Leu His Leu Pro
545                 550                 555                 560

Leu Ala Asp Pro Glu Val Val Thr Arg Pro Arg Gly Arg Gly Gly Pro
                565                 570                 575

Glu Ser Pro Pro Ser Asn Arg Tyr Ala Gly Asp Trp Ser Val Cys Gly
            580                 585                 590

Arg Asp Phe Leu Pro Cys Gly Arg Asp Phe Leu Ser Gly Pro Asp Tyr
        595                 600                 605

Asp His Val Thr Gly Ser Asp Ser Glu Asp Glu Asp Glu Glu Val Gly
    610                 615                 620

Glu Pro Arg Val Thr Gly Asp Phe Glu Asp Asp Phe Asp Ala Pro Phe
625                 630                 635                 640

Asn Pro His Leu Asn Leu Lys Asp Phe Asp Ala Leu Ile Leu Asp Leu
                645                 650                 655

Glu Arg Glu Leu Ser Lys Gln Ile Asn Val Cys Leu
            660                 665
```

<210> 50
<211> 475
<212> PRT
<213> Homo sapiens

<400> 50

```
Met Lys Val Glu Asp Leu Asn Val Cys Glu Pro Ala Ser Pro Ala Pro
1               5                  10                  15

Glu Ala Pro Ala Thr Ser Leu Leu Asn Asp Leu Lys Tyr Ser Pro Ser
            20                  25                  30

Glu Glu Glu Glu Val Thr Tyr Thr Val Ile Asn Gln Phe Gln Gln Lys
        35                  40                  45

Phe Gly Ala Ala Ile Leu His Ile Lys Lys Gln Asn Val Leu Ser Val
    50                  55                  60

Ala Ala Glu Gly Ala Asn Val Cys Arg His Gly Lys Leu Cys Trp Leu
65                  70                  75                  80

Gln Val Ala Thr Asn Cys Arg Val Tyr Leu Phe Asp Ile Phe Leu Leu
                85                  90                  95

Gly Ser Arg Ala Phe His Asn Gly Leu Gln Met Ile Leu Glu Asp Lys
            100                 105                 110

Arg Ile Leu Lys Val Ile His Asp Cys Arg Trp Leu Ser Asp Cys Leu
        115                 120                 125

Ser His Gln Tyr Gly Ile Leu Leu Asn Asn Val Phe Asp Thr Gln Val
    130                 135                 140

Ala Asp Val Leu Gln Phe Ser Met Glu Thr Gly Gly Tyr Leu Pro Asn
145                 150                 155                 160

Cys Ile Thr Thr Leu Gln Glu Ser Leu Ile Lys His Leu Gln Val Ala
                165                 170                 175

Pro Lys Tyr Leu Ser Phe Leu Glu Lys Arg Gln Lys Leu Ile Gln Glu
            180                 185                 190

Asn Pro Glu Val Trp Phe Ile Arg Pro Val Ser Pro Ser Leu Leu Lys
        195                 200                 205

Ile Leu Ala Leu Glu Ala Thr Tyr Leu Leu Pro Leu Arg Leu Ala Leu
    210                 215                 220
```

```
Leu Asp Glu Met Met Ser Asp Leu Thr Thr Leu Val Asp Gly Tyr Leu
225                 230                 235                 240

Asn Thr Tyr Arg Glu Gly Ser Ala Asp Arg Leu Gly Gly Thr Glu Pro
                245                 250                 255

Thr Cys Met Glu Leu Pro Glu Glu Leu Leu Gln Leu Lys Asp Phe Gln
            260                 265                 270

Lys Gln Arg Arg Glu Lys Ala Ala Arg Glu Tyr Arg Val Asn Ala Gln
        275                 280                 285

Gly Leu Leu Ile Arg Thr Val Leu Gln Pro Lys Lys Leu Val Thr Glu
    290                 295                 300

Thr Ala Gly Lys Glu Glu Lys Val Lys Gly Phe Leu Phe Gly Lys Asn
305                 310                 315                 320

Phe Arg Ile Asp Lys Ala Pro Ser Phe Thr Ser Gln Asp Phe His Gly
                325                 330                 335

Asp Val Asn Leu Leu Lys Glu Glu Ser Leu Asn Lys Gln Ala Thr Asn
            340                 345                 350

Pro Gln His Leu Pro Pro Thr Glu Glu Gly Glu Thr Ser Glu Asp Ser
        355                 360                 365

Ser Asn Lys Leu Ile Cys Thr Lys Ser Lys Gly Ser Glu Asp Gln Arg
    370                 375                 380

Ile Thr Gln Lys Glu His Phe Met Thr Pro Lys His Glu Phe Gln Ala
385                 390                 395                 400

Ser Leu Ser Leu Lys Glu Glu Thr Glu Gln Leu Leu Met Val Glu Asn
                405                 410                 415

Lys Glu Asp Leu Lys Cys Thr Lys Gln Ala Val Ser Met Ser Ser Phe
            420                 425                 430

Pro Gln Glu Thr Arg Val Ser Pro Ser Asp Thr Phe Tyr Pro Ile Arg
        435                 440                 445

Lys Thr Val Val Ser Thr Leu Pro Pro Cys Pro Ala Leu Glu Lys Ile
    450                 455                 460

Asp Ser Trp Ile Ser Pro Phe Leu Asn Leu Pro
```

465 470 475

<210> 51
<211> 1278
<212> PRT
<213> Homo sapiens

<400> 51

Met Thr Leu Thr Glu Arg Leu Arg Glu Lys Ile Ser Arg Ala Phe Tyr
1 5 10 15

Asn His Gly Leu Leu Cys Ala Ser Tyr Pro Ile Pro Ile Ile Leu Phe
20 25 30

Thr Gly Phe Cys Ile Leu Ala Cys Cys Tyr Pro Leu Leu Lys Leu Pro
35 40 45

Leu Pro Gly Thr Gly Pro Val Glu Phe Thr Thr Pro Val Lys Asp Tyr
50 55 60

Ser Pro Pro Pro Val Asp Ser Asp Arg Lys Gln Gly Glu Pro Thr Glu
65 70 75 80

Gln Pro Glu Trp Tyr Val Gly Ala Pro Val Ala Tyr Val Gln Gln Ile
85 90 95

Phe Val Lys Ser Ser Val Phe Pro Trp His Lys Asn Leu Leu Ala Val
100 105 110

Asp Val Phe Arg Ser Pro Leu Ser Arg Ala Phe Gln Leu Val Glu Glu
115 120 125

Ile Arg Asn His Val Leu Arg Asp Ser Ser Gly Ile Arg Ser Leu Glu
130 135 140

Glu Leu Cys Leu Gln Val Thr Asp Leu Leu Pro Gly Leu Arg Lys Leu
145 150 155 160

Arg Asn Leu Leu Pro Glu His Gly Cys Leu Leu Leu Ser Pro Gly Asn
165 170 175

Phe Trp Gln Asn Asp Trp Glu Arg Phe His Ala Asp Pro Asp Ile Ile
180 185 190

Gly Thr Ile His Gln His Glu Pro Lys Thr Leu Gln Thr Ser Ala Thr
195 200 205

```
Leu Lys Asp Leu Leu Phe Gly Val Pro Gly Lys Tyr Ser Gly Val Ser
    210                 215                 220

Leu Tyr Thr Arg Lys Arg Met Val Ser Tyr Thr Ile Thr Leu Val Phe
225                 230                 235                 240

Gln His Tyr His Ala Lys Phe Leu Gly Ser Leu Arg Ala Arg Leu Met
                245                 250                 255

Leu Leu His Pro Ser Pro Asn Cys Ser Leu Arg Ala Glu Ser Leu Val
            260                 265                 270

His Val His Phe Lys Glu Glu Ile Gly Val Ala Glu Leu Ile Pro Leu
        275                 280                 285

Val Thr Thr Tyr Ile Ile Leu Phe Ala Tyr Ile Tyr Phe Ser Thr Arg
    290                 295                 300

Lys Ile Asp Met Val Lys Ser Lys Trp Gly Leu Ala Leu Ala Ala Val
305                 310                 315                 320

Val Thr Val Leu Ser Ser Leu Leu Met Ser Val Gly Leu Cys Thr Leu
                325                 330                 335

Phe Gly Leu Thr Pro Thr Leu Asn Gly Gly Glu Ile Phe Pro Tyr Leu
            340                 345                 350

Val Val Val Ile Gly Leu Glu Asn Val Leu Val Leu Thr Lys Ser Val
        355                 360                 365

Val Ser Thr Pro Val Asp Leu Glu Val Lys Leu Arg Ile Ala Gln Gly
    370                 375                 380

Leu Ser Ser Glu Ser Trp Ser Ile Met Lys Asn Met Ala Thr Glu Leu
385                 390                 395                 400

Gly Ile Ile Leu Ile Gly Tyr Phe Thr Leu Val Pro Ala Ile Gln Glu
                405                 410                 415

Phe Cys Leu Phe Ala Val Val Gly Leu Val Ser Asp Phe Phe Leu Gln
            420                 425                 430

Met Leu Phe Phe Thr Thr Val Leu Ser Ile Asp Ile Arg Arg Met Glu
        435                 440                 445

Leu Ala Asp Leu Asn Lys Arg Leu Pro Pro Glu Ala Cys Leu Pro Ser
    450                 455                 460
```

```
Ala Lys Pro Val Gly Gln Pro Thr Arg Tyr Glu Arg Gln Leu Ala Val
465                 470                 475                 480

Arg Pro Ser Thr Pro His Thr Ile Thr Leu Gln Pro Ser Ser Phe Arg
                485                 490                 495

Asn Leu Arg Leu Pro Lys Arg Leu Arg Val Val Tyr Phe Leu Ala Arg
            500                 505                 510

Thr Arg Leu Ala Gln Arg Leu Ile Met Ala Gly Thr Val Val Trp Ile
        515                 520                 525

Gly Ile Leu Val Tyr Thr Asp Pro Ala Gly Leu Arg Asn Tyr Leu Ala
    530                 535                 540

Ala Gln Val Thr Glu Gln Ser Pro Leu Gly Glu Gly Ala Leu Ala Pro
545                 550                 555                 560

Met Pro Val Pro Ser Gly Met Leu Pro Pro Ser His Pro Asp Pro Ala
                565                 570                 575

Phe Ser Ile Phe Pro Pro Asp Ala Pro Lys Leu Pro Glu Asn Gln Thr
            580                 585                 590

Ser Pro Gly Glu Ser Pro Glu Arg Gly Gly Pro Ala Glu Val Val His
        595                 600                 605

Asp Ser Pro Val Pro Glu Val Thr Trp Gly Pro Glu Asp Glu Glu Leu
    610                 615                 620

Trp Arg Lys Leu Ser Phe Arg His Trp Pro Thr Leu Phe Ser Tyr Tyr
625                 630                 635                 640

Asn Ile Thr Leu Ala Lys Arg Tyr Ile Ser Leu Leu Pro Val Ile Pro
                645                 650                 655

Val Thr Leu Arg Leu Asn Pro Arg Glu Ala Leu Glu Gly Arg His Pro
            660                 665                 670

Gln Asp Gly Arg Ser Ala Trp Pro Pro Pro Gly Pro Ile Pro Ala Gly
        675                 680                 685

His Trp Glu Ala Gly Pro Lys Gly Pro Gly Gly Val Gln Ala His Gly
    690                 695                 700
```

```
Asp Val Thr Leu Tyr Lys Val Ala Ala Leu Gly Leu Ala Thr Gly Ile
705                 710                 715                 720

Val Leu Val Leu Leu Leu Leu Cys Leu Tyr Arg Val Leu Cys Pro Arg
                725                 730                 735

Asn Tyr Gly Gln Leu Gly Gly Gly Pro Gly Arg Arg Arg Arg Gly Glu
            740                 745                 750

Leu Pro Cys Asp Asp Tyr Gly Tyr Ala Pro Pro Glu Thr Glu Ile Val
        755                 760                 765

Pro Leu Val Leu Arg Gly His Leu Met Asp Ile Glu Cys Leu Ala Ser
    770                 775                 780

Asp Gly Met Leu Leu Val Ser Cys Cys Leu Ala Gly His Val Cys Val
785                 790                 795                 800

Trp Asp Ala Gln Thr Gly Asp Cys Leu Thr Arg Ile Pro Arg Pro Gly
                805                 810                 815

Gln Arg Arg Asp Ser Gly Val Gly Ser Gly Leu Glu Ala Gln Glu Ser
            820                 825                 830

Trp Glu Arg Leu Ser Asp Gly Gly Lys Ala Gly Pro Glu Glu Pro Gly
        835                 840                 845

Asp Ser Pro Pro Leu Arg His Arg Pro Arg Gly Pro Pro Pro Pro Ser
    850                 855                 860

Leu Phe Gly Asp Gln Pro Asp Leu Thr Cys Leu Ile Asp Thr Asn Phe
865                 870                 875                 880

Ser Ala Gln Pro Arg Ser Ser Gln Pro Thr Gln Pro Glu Pro Arg His
                885                 890                 895

Arg Ala Val Cys Gly Arg Ser Arg Asp Ser Pro Gly Tyr Asp Phe Ser
            900                 905                 910

Cys Leu Val Gln Arg Val Tyr Gln Glu Glu Gly Leu Ala Ala Val Cys
        915                 920                 925

Thr Pro Ala Leu Arg Pro Pro Ser Pro Gly Pro Val Leu Ser Gln Ala
    930                 935                 940

Pro Glu Asp Glu Gly Gly Ser Pro Glu Lys Gly Ser Pro Ser Leu Ala
945                 950                 955                 960
```

```
Trp Ala Pro Ser Ala Glu Gly Ser Ile Trp Ser Leu Glu Leu Gln Gly
                965                 970                 975

Asn Leu Ile Val Val Gly Arg Ser Ser Gly Arg Leu Glu Val Trp Asp
            980                 985                 990

Ala Ile Glu Gly Val Leu Cys Cys  Ser Ser Glu Glu Val  Ser Ser Gly
        995                 1000                1005

Ile Thr  Ala Leu Val Phe Leu  Asp Lys Arg Ile Val  Ala Ala Arg
    1010                1015                1020

Leu Asn  Gly Ser Leu Asp Phe  Phe Ser Leu Glu Thr  His Thr Ala
    1025                1030                1035

Leu Ser  Pro Leu Gln Phe Arg  Gly Thr Pro Gly Arg  Gly Ser Ser
    1040                1045                1050

Pro Ala  Ser Pro Val Tyr Ser  Ser Ser Asp Thr Val  Ala Cys His
    1055                1060                1065

Leu Thr  His Thr Val Pro Cys  Ala His Gln Lys Pro  Ile Thr Ala
    1070                1075                1080

Leu Lys  Ala Ala Ala Gly Arg  Leu Val Thr Gly Ser  Gln Asp His
    1085                1090                1095

Thr Leu  Arg Val Phe Arg Leu  Glu Asp Ser Cys Cys  Leu Phe Thr
    1100                1105                1110

Leu Gln  Gly His Ser Gly Ala  Ile Thr Thr Val Tyr  Ile Asp Gln
    1115                1120                1125

Thr Met  Val Leu Ala Ser Gly  Gly Gln Asp Gly Ala  Ile Cys Leu
    1130                1135                1140

Trp Asp  Val Leu Thr Gly Ser  Arg Val Ser His Val  Phe Ala His
    1145                1150                1155

Arg Gly  Asp Val Thr Ser Leu  Thr Cys Thr Thr Ser  Cys Val Ile
    1160                1165                1170

Ser Ser  Gly Leu Asp Asp Leu  Ile Ser Ile Trp Asp  Arg Ser Thr
    1175                1180                1185
```

```
Gly Ile  Lys Phe Tyr Ser Ile  Gln Gln Asp Leu Gly  Cys Gly Ala
    1190                 1195                 1200

Ser Leu  Gly Val Ile Ser Asp  Asn Leu Leu Val Thr  Gly Gly Gln
    1205                 1210                 1215

Gly Cys  Val Ser Phe Trp Asp  Leu Asn Tyr Gly Asp  Leu Leu Gln
    1220                 1225                 1230

Thr Val  Tyr Leu Gly Lys Asn  Ser Glu Ala Gln Pro  Ala Arg Gln
    1235                 1240                 1245

Ile Leu  Val Leu Asp Asn Ala  Ala Ile Val Cys Asn  Phe Gly Ser
    1250                 1255                 1260

Glu Leu  Ser Leu Val Tyr Val  Pro Ser Val Leu Glu  Lys Leu Asp
    1265                 1270                 1275
```

<210> 52
<211> 123
<212> PRT
<213> Homo sapiens

<400> 52

```
Met Ile Leu Ala Val His Leu Lys Arg Phe Lys Tyr Met Asp Gln Leu
1               5                   10                  15

His Arg Tyr Thr Lys Leu Ser Tyr Arg Val Val Phe Pro Leu Glu Leu
            20                  25                  30

Arg Leu Phe Asn Thr Ser Gly Asp Ala Thr Asn Pro Asp Arg Met Tyr
        35                  40                  45

Asp Leu Val Ala Val Val Val His Cys Gly Ser Gly Pro Asn Arg Gly
    50                  55                  60

His Tyr Ile Ala Ile Val Lys Ser His Asp Phe Trp Leu Leu Phe Asp
65                  70                  75                  80

Asp Asp Ile Val Glu Lys Ile Asp Thr Gln Ala Ile Glu Glu Phe Tyr
                85                  90                  95

Gly Leu Thr Ser Asp Thr Gln Arg Thr Leu Ser Leu Val Thr Ser Phe
            100                 105                 110

Ser Ile Ser Leu Gly Thr Glu Gly Glu Pro Arg
        115                 120
```

<210> 53
<211> 370
<212> PRT
<213> Homo sapiens

<400> 53

Met Glu Ile Leu Met Thr Val Ser Lys Phe Ala Ser Ile Cys Thr Met
1 5 10 15

Gly Ala Asn Ala Ser Ala Leu Glu Lys Glu Ile Gly Pro Glu Gln Phe
20 25 30

Pro Val Asn Glu His Tyr Phe Gly Leu Val Asn Phe Gly Asn Thr Cys
35 40 45

Tyr Cys Asn Ser Val Leu Gln Ala Leu Tyr Phe Cys Arg Pro Phe Arg
50 55 60

Glu Lys Val Leu Ala Tyr Lys Ser Gln Pro Arg Lys Lys Glu Ser Leu
65 70 75 80

Leu Thr Cys Leu Ala Asp Leu Phe His Ser Ile Ala Thr Gln Lys Lys
85 90 95

Lys Val Gly Val Ile Pro Pro Lys Lys Phe Ile Thr Arg Leu Arg Lys
100 105 110

Glu Asn Glu Leu Phe Asp Asn Tyr Met Gln Gln Asp Ala His Glu Phe
115 120 125

Leu Asn Tyr Leu Leu Asn Thr Ile Ala Asp Ile Leu Gln Glu Glu Arg
130 135 140

Lys Gln Glu Lys Gln Asn Gly Arg Leu Pro Asn Gly Asn Ile Asp Asn
145 150 155 160

Glu Asn Asn Asn Ser Thr Pro Asp Pro Thr Trp Val Asp Glu Ile Phe
165 170 175

Gln Gly Thr Leu Thr Asn Glu Thr Arg Cys Leu Thr Cys Glu Thr Ile
180 185 190

Ser Ser Lys Asp Glu Asp Phe Leu Asp Leu Ser Val Asp Val Glu Gln
195 200 205

Asn Thr Ser Ile Thr His Cys Leu Arg Gly Phe Ser Asn Thr Glu Thr
210 215 220

Leu Cys Ser Glu Tyr Lys Tyr Tyr Cys Glu Glu Cys Arg Ser Lys Gln
225 230 235 240

Glu Ala His Lys Arg Met Lys Val Lys Lys Leu Pro Met Ile Leu Ala
245 250 255

Leu His Leu Lys Arg Phe Lys Tyr Met Asp Gln Leu His Arg Tyr Thr
260 265 270

Lys Leu Ser Tyr Arg Val Val Phe Pro Leu Glu Leu Arg Leu Phe Asn
275 280 285

Thr Ser Gly Asp Ala Thr Asn Pro Asp Arg Met Tyr Asp Leu Val Ala
290 295 300

Val Val Val His Cys Gly Ser Gly Pro Asn Arg Gly His Tyr Ile Ala
305 310 315 320

Ile Val Lys Ser His Asp Phe Trp Leu Leu Phe Asp Asp Asp Ile Val
325 330 335

Glu Lys Ile Asp Ala Gln Ala Ile Glu Glu Phe Tyr Gly Leu Thr Ser
340 345 350

Asp Ile Ser Lys Asn Ser Glu Ser Gly Tyr Ile Leu Phe Tyr Gln Ser
355 360 365

Arg Asp
370

<210> 54
<211> 520
<212> PRT
<213> Homo sapiens

<400> 54

Met Gly Pro Gln Arg Arg Leu Ser Pro Ala Gly Ala Ala Leu Leu Trp
1 5 10 15

Gly Phe Leu Leu Gln Leu Thr Ala Ala Gln Glu Ala Ile Leu His Ala
20 25 30

Ser Gly Asn Gly Thr Thr Lys Asp Tyr Cys Met Leu Tyr Asn Pro Tyr
35 40 45

Trp Thr Ala Leu Pro Ser Thr Leu Glu Asn Ala Thr Ser Ile Ser Leu

50 55 60

Met Asn Leu Thr Ser Thr Pro Leu Cys Asn Leu Ser Asp Ile Pro Pro
65 70 75 80

Val Gly Ile Lys Ser Lys Ala Val Val Val Pro Trp Gly Ser Cys His
85 90 95

Phe Leu Glu Lys Ala Arg Ile Ala Gln Lys Gly Gly Ala Glu Ala Met
100 105 110

Leu Val Val Asn Asn Ser Val Leu Phe Pro Pro Ser Gly Asn Arg Ser
115 120 125

Glu Phe Pro Asp Val Lys Ile Leu Ile Ala Phe Ile Ser Tyr Lys Asp
130 135 140

Phe Arg Asp Met Asn Gln Thr Leu Gly Asp Asn Ile Thr Val Lys Met
145 150 155 160

Tyr Ser Pro Ser Trp Pro Asn Phe Asp Tyr Thr Met Val Val Ile Phe
165 170 175

Val Ile Ala Val Phe Thr Val Ala Leu Gly Gly Tyr Trp Ser Gly Leu
180 185 190

Val Glu Leu Glu Asn Leu Lys Ala Val Thr Thr Glu Asp Arg Glu Met
195 200 205

Arg Lys Lys Lys Glu Glu Tyr Leu Thr Phe Ser Pro Leu Thr Val Val
210 215 220

Ile Phe Val Val Ile Cys Cys Val Met Met Val Leu Leu Tyr Phe Phe
225 230 235 240

Tyr Lys Trp Leu Val Tyr Val Met Ile Ala Ile Phe Cys Ile Ala Ser
245 250 255

Ala Met Ser Leu Tyr Asn Cys Leu Ala Ala Leu Ile His Lys Ile Pro
260 265 270

Tyr Gly Gln Cys Thr Ile Ala Cys Arg Gly Lys Asn Met Glu Val Arg
275 280 285

Leu Ile Phe Leu Ser Gly Leu Cys Ile Ala Val Ala Val Val Trp Ala
290 295 300

Val Phe Arg Asn Glu Asp Arg Trp Ala Trp Ile Leu Gln Asp Ile Leu
305 310 315 320

Gly Ile Ala Phe Cys Leu Asn Leu Ile Lys Thr Leu Lys Leu Pro Asn
325 330 335

Phe Lys Ser Cys Val Ile Leu Leu Gly Leu Leu Leu Leu Tyr Asp Val
340 345 350

Phe Phe Val Phe Ile Thr Pro Phe Ile Thr Lys Asn Gly Glu Ser Ile
355 360 365

Met Val Glu Leu Ala Ala Gly Pro Phe Gly Asn Asn Glu Lys Leu Pro
370 375 380

Val Val Ile Arg Val Pro Lys Leu Ile Tyr Phe Ser Val Met Ser Val
385 390 395 400

Cys Leu Met Pro Val Ser Ile Leu Gly Phe Gly Asp Ile Ile Val Pro
405 410 415

Gly Leu Leu Ile Ala Tyr Cys Arg Arg Phe Asp Val Gln Thr Gly Ser
420 425 430

Ser Tyr Ile Tyr Tyr Val Ser Ser Thr Val Ala Tyr Ala Ile Gly Met
435 440 445

Ile Leu Thr Phe Val Val Leu Val Leu Met Lys Lys Gly Gln Pro Ala
450 455 460

Leu Leu Tyr Leu Val Pro Cys Thr Leu Ile Thr Ala Ser Val Val Ala
465 470 475 480

Trp Arg Arg Lys Glu Met Lys Lys Phe Trp Lys Gly Asn Ser Tyr Gln
485 490 495

Met Met Asp His Leu Asp Cys Ala Thr Asn Glu Glu Asn Pro Val Ile
500 505 510

Ser Gly Glu Gln Ile Val Gln Gln
515 520

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number
WO 2004/083389 A3

(51) International Patent Classification:
G01N 33/566 (2006.01) *C12Q 1/70* (2006.01)
G01N 33/53 (2006.01)

(21) International Application Number:
PCT/US2004/007626

(22) International Filing Date: 12 March 2004 (12.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/454,469	13 March 2003 (13.03.2003)	US
60/470,728	14 May 2003 (14.05.2003)	US
60/479,769	19 June 2003 (19.06.2003)	US
60/479,795	19 June 2003 (19.06.2003)	US

(71) Applicant *(for all designated States except US)*: **EXELIXIS INC.** [US/US]; 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FRANCIS-LANG, Helen** [GB/US]; 1782 Pacific Avenue, #2, San Francisco, CA 94109 (US). **WINTER, Christopher, G.** [US/US]; 641 Homer Avenue, Palo Alto, CA 94301 (US). **VENTURA, Richard, Benn, Abegania** [US/US]; 290 Bay Ridge Drive, Daly City, CA 94014 (US). **BJERKE, Lynn, Margaret** [US/US]; 728 Alabama Street, #201, San Francisco, CA 94110 (US). **ZHANG, HaiGuang** [US/US]; 4833 El Grande Place, El Sobrante, CA 94083 (US). **ADAMKEWICZ, Joanne, I.** [US/US]; 1249 Rhode Island Street, San Francisco, CA 94107 (US). **HAI, Bing** [CN/US]; 410 Promenade Lane, Redwood City, CA 94065 (US). **LICKTEIG, Kim** [US/US]; 1921 Grove Street, San Francisco, CA 94117 (US). **NICOLL, Monique** [US/US]; 224 Naomi Avenue, Pacifica, CA 94044 (US).

(74) Agents: **SHAYESTEH, Laleh** et al.; Exelixis, Inc., 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
12 October 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

(57) Abstract: Human MBCAT genes are identified as modulators of the beta-catenin pathway, and thus are therapeutic targets for disorders associated with defective beta-catenin function. Methods for identifying modulators of beta-catenin, comprising screening for agents that modulate the activity of MBCAT are provided.

WO 2004/083389 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/07626

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **G01N 33/566**(2006.01),**33/53**(2006.01);**C12Q 1/70**(2006.01)

USPC: 436/501;435/5,7.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 436/501; 435/5,7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN DATABASE (cancerlit, biosis, confsci, scisearch, embase, caplus, uspatfull, pctfull, dissabs), WEST, PUBMED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OLOUNI et al Modulation of Wnt3a-Mediated Nuclear Beta-Catenin Accumulation and Activation by Integrin-Linked Kinase in Mammalian Cells. Oncogene. June 26, 2006; [Epub ahead of print], pages 1-11	1-24
A	CLAPPER et al Beta-Catenin-Mediated Signaling: A Molecular Target for Early Chemopreventive Intervention. Mutat Res. November 2004 , Vol. 555, No. 1-2, pages 97-105.	1-24

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
24 July 2006 (24.07.2006)

Date of mailing of the international search report
24 AUG 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Christopher H. Yaen

Telephone No. 571-272-0600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/07626

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LU et al Isoprenylcysteine Carboxyl Methyltransferase Modulates Endothelial Monolayer Permeability: Involvement of RhoA Carboxyl Methylation. Circ Res. February 2004, Vol. 94, No. 3, pages 306-315.	1-24